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ORIGINAL ARTICLE

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- Diagnostic Yield And Safety Profile Of Alligator Versus Cup Forceps To Obtain Endobronchial Tissue In Patients Suspected To Have Bronchogenic Carcinoma
- Reduction In Central Line Associated Blood Stream Infection (CLABSI) In NICU: A Quality Improvement Study
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Original Article

Seroprevalence of Hepatitis A and Hepatitis E infection amongst clinically suspected cases of Acute Viral Hepatitis at tertiary care hospital, Jaipur Rajasthan

Shikha Soni*, Manju Yadav, Rameshwari Bithu***, Abhilasha Kumawat****, Ruchi Jain*****, S.K. Singh*****

ABSTRACT

Background: Viral hepatitis is a significant cause of morbidity in India and is now equated as a threat comparable to the ‘‘big three’’ communicable diseases viz. AIDS, malaria, and tuberculosis. The primary aim of present study was to determine the seroprevalence of Hepatitis A, Hepatitis E and co-infection amongst the patient’s suspected with signs and symptoms of acute viral hepatitis and also to determine the demographic pattern and seasonal distribution of viral hepatitis infection. **Material and Method:** Two hundred fifty eight patients with symptoms of acute viral hepatitis were taken and single centre, hospital based, cross-sectional observational study was done over period of one year.**Result and Conclusion:** Out of 258 patients, HAV IgM antibody was detected in 33 patients (seroprevalence-12.7%), HEV IgM antibody was detected in 28 (seroprevalence-10.9%) and co-infection was detected in 6 patients (seroprevalence 2.3%). Seroprevalence of HAV was more common in males (57.60%) while of Hepatitis E Virus was more common in females (67.9%). Maximum number of patients of Hepatitis A virus were in age group 0-20 years while Hepatitis E virus were in age group 21-40 years. Majority of patients were residing in slum area (39.53%). Most of the cases were seen in months of August to October i.e. during monsoon season and were from low socioeconomic group who did not have facility for safe drinking water. A community programme like "Swatch Bharat Abhiyan" and other surveillance programme by hospitals with multipronged approach of screening are expected to reduce incidence of infected viral Hepatitis.

Keywords: Acute Hepatitis, Gastroenteritis, Seasonal Trend, Water borne diseases.

INTRODUCTION

Viral hepatitis is a significant cause of morbidity in India and is now equated as a threat comparable to the ‘‘big three’’ communicable diseases viz. AIDS, malaria and tuberculosis[1]. The World Health Organization estimates that there are 1.4 million cases of hepatitis A globally each year resulting in approximately 7000 deaths[2]. In comparison, there are an estimated 20 million hepatitis E infections each year leading to 3.3 million symptomatic cases and around 44,000 death[3]. All cases of acute viral hepatitis are caused by one of five viral agents, among all the enteric pathogens i.e. Hepatitis A and Hepatitis E viruses are epidemiologically the most important ones[4]. Both viruses cause sporadic infections as well as epidemic outbreaks of acute viral hepatitis.

HAV spreads via the faecal-oral route and is associated with poor sanitary and bad hygienic conditions. HAV infection is common during childhood and usually results in mild anicteric hepatitis[5]. India is categorised as a hyper-endemic country for HAV because HAV is highly prevalent among the paediatric age groups as exposure to the Hepatitis A virus typically occurs early in life when the infection is often subclinical. HEV also primarily spread via the faeco-oral route and is an enterically transmitted pathogen like HAV[6]. HEV is the commonest causative agent of acute viral hepatitis and is responsible for epidemics, focal outbreaks as well as sporadic infections[7]. During an outbreak, it is observed that pregnant women have a higher likelihood of getting infected (12–20%) with HEV and have a higher propensity to develop acute liver failure (ALF) (10–22%) when compared to non-pregnant females (1–2%) [8].

Exposure rate of HAV and HEV vary widely between different geographical regions, predominantly influenced by socioeconomic factors. Despite being a major health challenge, not many studies exploring the prevalence, aetiology, and clinic-epidemiological profile of acute viral hepatitis are available in India. Though few studies describing the incidence or aetiology of viral hepatitis have been reported from various parts of the country, there are not many studies conducted in the state of Rajasthan. The primary aim of present study was to determine the seroprevalence of Hepatitis A and Hepatitis E viruses among patients presenting with symptoms of acute viral

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hepatitis. In addition, the present study was conducted to determine the frequency, seasonal distribution, pattern of viral hepatitis infection, associated clinical features and outcome among clinically suspected acute viral hepatitis cases presented at SMS Hospital, Jaipur, Rajasthan.

MATERIAL AND METHODS

The present study was conducted in Central Laboratory of a Medical College and attached tertiary care Hospitals. The data collection was initiated after the research protocol was approved by the Institute's Ethical Committee. At the time of enrolment, informed written consent was obtained from participants and a performa was filled which consisted of socio-demographic characteristics & clinical history of study participants. The study was conducted over a period of one year from May 2021- April 2022. Two hundred fifty eight patients were enrolled in the study presenting with sign and symptoms of jaundice, fever, pain abdomen, dark urine, nausea and vomiting which were considered as suspected cases of acute viral hepatitis.

Sample Collection and Processing: 5ml of whole blood was collected by venepuncture into a sterile plain vial and allowed to clot. The clotted blood sample was centrifuged at 3000 rpm for 10 minutes to obtain serum. The serum was then transferred into a separate tube and then stored at 2-8°C in refrigerator and tested by following methods.

i. **HAV IgM antibody:** HAV IgM Antibody was detected by commercially available ELISA (BIONEOVAN Co. Ltd-China). Tests were performed in accordance with manufactures instruction.

ii. **HEV IgM antibody:** HEV IgM Antibody was detected by commercially available ELISA (BIONEOVAN Co. Ltd-China). Tests were performed in accordance with manufactures instruction.

Statistical Analysis Plan: All the data were collected in a paper-based data collection form. Thereafter, the data were coded and entered in Microsoft Excel. The coded data were imported into Stata 17.1 version for analysis. For the continuous data, the mean, median, mode, and standard deviation was calculated.

RESULTS

Blood sample were collected from patients and tested. HAV IgM antibody was detected in 33 patients (12.7%), HEV IgM antibody was detected in 28(10.9%) and co-infection was detected in 6 patients (2.3%).

Among 33 patients tested positive for Hepatitis A, 19 (57.60%) were male and 14 (42.40%) were female (P = 0.403). The maximum number of patients of Hepatitis-A IgM antibody belonged to age group 11-20 years (39.4%) followed by 0-10 years (33.3%). Hepatitis-A IgM antibody was detected in younger age group (p-value = 0.001). In subclinical infection, ingestion of contaminated food or water imported from endemic areas, and/or contamination linked to environmental reservoir may serve as a reason for paediatric age group susceptibility to infection.

Among 28 patients tested positive for Hepatitis E; 19 (67.90%) were female and 9 (32.1%) were male (p=0.034). Among the 28 participants tested for Hepatitis E: 60.7% were aged between 21-40 years, and 21.4% were aged between 41-60 years of age.

The difference in distribution of Hepatitis A (p=0.02) and Hepatitis E (p=0.017) patients as per their residence was statistically significant which correspond to more cases found in people residing in slum areas owing to poor sanitation.

Out of 33 HAV positive patients, high seroprevalence were observed in low socioeconomic status group 15 (45.50%) followed by 8 (24.20%) in low or middle socioeconomic status group. The distribution of HAV patients as per their socioeconomic status was statistically significant (p=0.032). Among the 28 HEV positive patients, high seroprevalence were analyzed in low socioeconomic status (SES) 12 (42.80%) followed by 8 (28.60%) low middle socioeconomic status. There was no statistically significant difference found in HEV according to socioeconomic status (p=0.108).

High seroprevalence of hepatitis A and hepatitis E was found in piped drinking water followed by tank drinking water but there was no statistically significant difference found according to the source of drinking water (HAV; p=0.08 and HEV; p=0.095).

As shown in Table 2, out of 33 HAV positive; majority of positive patients were found in month of September (8, 18.60%) and October (8, 17.78%) and out of 28 HEV positive; majority of positive patients were found in September (7, 16.28%) and August (6, 15.79%) which correlates with pre-monsoon season in India.

DISCUSSION

HAV and HEV type of viral Hepatitis emerged as a major concern regarding public health in developing nations, specifically where there are unsystematic waste management facilities and poor supply of safe drinking water.

In present study, HAV IgM antibodies were detected in 33 patients (seroprevalence-12.7%) whereas HEV IgM antibody were detected in 28 patients (seroprevalence-10.9%). HAV is considered as a most common cause of viral hepatitis on global basis and present study also reported higher prevalence of HAV in comparison to HEV and same observation was analysed by Joon A et al[9], Agarwal M et al[10], Agarwal S et al[11], Murhekar MV et al[12], Chatterjee S et al.[13] and Patel P et al[14]. Variation in

seroprevalence of both HAV and HEV in different regions might be due to personal hygiene, sanitation, and sources of water supply. It may also due to the type of diagnostic kit utilized by the testing laboratory. Although, antibodies against different strains may also vary in persistence. Out of all Hepatitis A patients, 19 (57.60%) were male and 14 (42.40%) were female (P = 0.403). Present study is similar to conducted by Joon A et al[9] prevalence of males 68% were more than females 32% which was also in line with results of studies conducted by Mittal et al.[15], Antony and Celine[16], Sarangi et al.[17], Barrientos-Gutierrez et al.[18], Manmohan et al.[19], Al-Naaimi et al.[20], Kamal et al.[21], Dhamdhere and Nadkarni[22], and Mishra et al.[23] Maximum patients of Hepatitis A belonged to age group 11-20 years (39.4%) followed by 0-10 years (33.3%). The difference in distribution of age group among patients diagnosed with Hepatitis A was statistically significant (p=0.001). Like our findings, studies by Joon et al.[9], Mittal et al.[15], Sarangi et al.[17], Arora et al.[24], Chandra et al.[25], and Sebastian et al.[26] also reported that acute Hepatitis A infection was predominantly seen among children or adolescent. However, studies by Antony and Celine[16], Davaalkham et al.[27], and Arankalle et al.[28] reported a shift of HAV infection from paediatric population to adults, might be due to improved standard of living. Highest seroperevalence of HAV was analysed in lower socioeconomic status group patients (45.5%) followed by low middle socioeconomic status group patients (24.2%). The difference in distribution of HAV patients as per their socioeconomic status was statistically significant (p=0.032). Similar to our study, Rath CP et al.[29] reported that HAV exposure was also significantly high among low socioeconomic status patients 53.9% in comparison to high/middle socioeconomic status 33.3%. Ahmed M et al.[30] found significantly lower HAV seroprevalence in high socioeconomic status vs. low socioeconomic status populations (68.8 vs. 79.7%, $p < 0.05$). Our results are consistent with the study conducted by Rath CP et al.[29] i.e. maximum number of HAV and HEV patients belonged to lower socioeconomic status and lived in the area where sanitation facilities and water supply was inappropriate.[29]

HEV IgM antibody were detected in 28 patients (seroprevalence -10.9%). Out of all 28 patients positive for Hepatitis E; 19 (67.90%) were female and 9 (32.1%) were male. Statistically significant difference was found according to gender (P = 0.034). Our results were consistent with Samadhar et al.[31], Agarwal S et al.[11] and Bansal Y[32] et al who also reported higher seroprevalence of HEV in female patients. Among the 28 patients tested for Hepatitis E: 60.70% were aged between 21-40 years, and 21.43% were aged between 41-60 years of age. The HEV IgM antibodies were detected more in elder age groups. The difference in distribution of age group among patients diagnosed with Hepatitis E was statistically significant (p=0.010). Priyadarshini et al.[33] reported that the seropositivity of HEV in adults were (93.7%). Joon et al.[9], Murhekar MV et al[12], Mittal et al.[15], Sarangi et al.[17], Arora et al.[24], Chandra et al.[25], and Sebastian et al.[26] also reported HEV positivity was higher in patients more than 20 years which resembled the findings of present study. In the present study high seroprevalence of HEV was also noted from low socioeconomic status 42.80% followed by 28.60% low middle socioeconomic status. There is no statistically significant difference found in HEV according to socioeconomic status. (p=0.108).

The difference in distribution of HAV and HEV patients as per their residence was statistically significant (p=0.02 and p=0.017 respectively) and more among slum area residents.

In most positive patients of HAV (September 18.60% followed by October 17.78%, November 18.75%) and HEV (September 16.28%, October 11.11%, and November 12.50%) were seen near the time of monsoon season. Chatterjee S et al.[13] reported that seasonal distribution of HAV and HEV infections followed a bimodal peak pattern with peaks reported in the pre-monsoon and rainy seasons. Kumar M et al.[34] reported that HAV cases were seen throughout the year with peaks of HAV cases in May, July and August and HEV cases in the month from January to May. Our results were consistent with Chatterjee S et al[13] and Samaddar A et al.[31] who reported higher seroprevalence of HAV and HEV in pre-monsooon and rainy season.

Co-infection was detected in 6 patients (seroprevalence-2.3%). The rate of co-infection in present study was 2.3% which is in similar to a study done by Samaddar A et al.[31] who reported co-infection in 2.07% of patients.

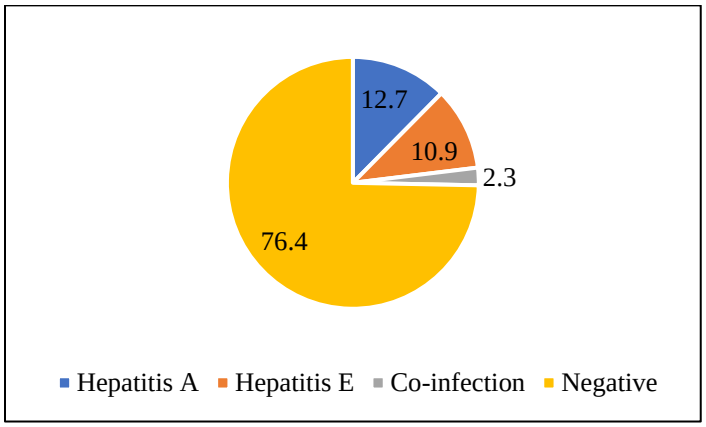

Figure 1: Distribution of patients according to seropositivity of HAV, HEV and Co infection

Table 1: Seroprevalence of HAV and HEV according to Demography and Socioeconomic status

Variable	Total Tested	HAV	HEV
		Positive Number (%)	Positive Number (%)
Gender			
Male	131	19 (57.6)	9 (32.1)
Female	127	14 (42.4)	19 (67.9)
Age Group			
0-10	54	11 (33.3)	1 (3.6)
11-20	51	13(39.4)	4 (14.3)
21-40	87	6 (18.2)	17 (60.7)
41-60	53	1 (3.0)	6 (21.4)
>60	13	2(6.0)	0 (0.0)
Residence			
Slum	102	19 (57.6)	18 (64.3)
Rural	85	11 (33.3)	6 (21.4)
Urban	71	3 (9.1)	4 (14.3)
p-value	-	**0.020**	**0.017**
Socioeconomic Status			
Upper Middle	48	3(9.1)	3(10.7)
Middle	72	7(21.2)	5(17.9)
Low Middle	73	8(24.2)	8(28.6)
Low	65	15(45.5)	12(42.8)
p-value	-	**0.032**	**0.108**
Source of Drinking water			
Bore-well	50	6(18.2)	6(21.4)
Piped	55	10(30.30)	8(28.6)
Tank	57	8(24.20)	6(21.4)
Handpump	52	6(18.2)	5(17.9)
Filtered	44	3(9.10)	3(10.7)
p-value	-	**0.08**	**0.095**

Table 2: **Seroprevalence of HAV according to the time of year**

Month	HAV Positive (N=33)		Total Number of patients tested
	Number of HAV positive patients	%	
May 21	1	7.69	13
June 21	2	10.00	20
July 21	3	11.11	27
August 21	6	15.79	38
September 21	8	18.60	43
October 21	8	17.78	45
November 21	3	18.75	16
December 21	1	5.56	18
January 22	0	0.00	8
February 22	0	0.00	8
March 22	0	0.00	10
April 22	1	8.33	12
Total	33		258

Table 3: **Seroprevalence of HEV according to the time of year**

Month	HEV **Positive (N=28)**		Total Number of patients tested
	Number of HEV positive Patients	%	
May 21	1	7.69	13
June 21	1	5.00	20
July 21	3	11.11	27
August 21	6	15.79	38
September 21	7	16.28	43
October 21	5	11.11	45
November 21	2	12.50	16
December 21	1	5.56	18
January 22	0	0.00	8
February 22	0	0.00	8
March 22	1	10.00	10
April 22	1	8.33	12
Total	28		258

CONCLUSION

Role of vaccination plays a vital role as this study shows high prevalence of HAV among children and low in adults. Purpose of study clearly indicate that Hepatitis A and Hepatitis E are preventable diseases as more cases were found from people residing in slum areas with poor water supply, hence improving sanitation can aid in prevention and it may lead to grave consequences, especially in pregnant women, so screening protocols should be set up for all pregnant females as part of the antenatal management for early detection of the cases.

The incidence of both Hepatitis A and E showed seasonal trend with highest cases detected around the time of monsoon and lowest during the winter and spring season. Public health problems associated with the feaco-oral transmission of viral hepatitis requires implementation of stronger measures to prevent faecal contamination of food and water.

A community program like “Swatchh Bharat Abhiyan” and a surveillance program by hospitals with multipronged approach of screening, treatment and immunization are expected to reduce incidences of infective viral hepatitis.

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Original Article

Diagnostic yield and safety profile of alligator versus cup forceps to obtain endobronchial tissue in patients suspected to have bronchogenic carcinoma

Vinayak Mangal*, Ashish Kumar Singh, Asha M A***, Nithin N. Shenoy******

ABSTRACT

INTRODUCTION: Endobronchial biopsy (EBB) is a procedure of obtaining tissue for pathological analysis, performed during bronchoscopy using different forceps. One of the most common indications of performing EBB is for the diagnosis of bronchogenic carcinoma. Our study aimed to compare alligator and cup forceps in terms of size of tissue obtained and severity of bleeding observed during the procedure.

METHODOLOGY: We conducted a cross sectional, hospital based, comparative study in 80 patients over a period of 1 year (July 2018 to June 2019). Patients with computed tomography (CT) of chest suggestive of endobronchial lesion were included in the study and underwent EBB using alligator or cup forceps alternatively, and results were compared.

RESULTS: Of total 80 patients, 40 each were biopsied using alligator and cup forceps. Biopsy tissue obtained was significantly smaller with cup forceps ($p = 0.046$), but diagnostic yield was same between the two forceps (97.5%). Difference in severity of bleeding was not statistically significant between the forceps ($p = 0.5511$). Most common type of bronchogenic carcinoma obtained was squamous cell carcinoma (45%).

CONCLUSION: Our study favours alligator forceps use over cup forceps, as larger tissue size and lesser severity of bleeding was observed with the former. However, larger randomized controlled trials are needed to validate the findings.

Keywords: endobronchial biopsy, forceps, bronchogenic carcinoma, bleeding.

INTRODUCTION

Endobronchial biopsy (EBB) is a commonly performed procedure during bronchoscopy.[1] In this, endobronchial samples are obtained with the help of biopsy forceps for pathological analysis.[1] Most common indications for EBB is to diagnose bronchogenic carcinoma, sarcoidosis, endobronchial tuberculosis (TB) and endobronchial metastases.[1] The aim of EBB is to obtain pieces of tissues that contain relevant structures and cells for histological analysis.[1]

Most widely available forceps for EBB include cup and alligator forceps with or without spokes.[1] They are available in range of sizes which are compatible with bronchoscope channel sizes from 1.2 to 3.7 mm.[1]

Complications can occur during and following EBB. Major complications include death, cardiopulmonary arrest, myocardial infarction, pneumonia, airways obstruction severe enough to require therapy, pulmonary haemorrhage requiring transfusion, seizures and stroke.[2] Minor complications include bleeding in amounts greater than 50ml but not requiring transfusion, vaso-vagal reaction, mild airways obstruction and arrhythmia.[2]

Several risk factors have been associated with bleeding during bronchoscopy, including immunosuppression, thrombocytopenia, pulmonary arterial hypertension, and mechanical ventilation.[3]

There have not been any study comparing results of alligator and cup forceps in endobronchial biopsy. Our study aimed to compare the two forceps in terms of size of tissue obtained (both, as compared to forceps blade size and by pathological review), yield and complications (in terms of bleeding during endobronchial biopsy, graded according to measures used to stop bleeding).

METHODOLOGY

STUDY DESIGN

It was a single centre, tertiary hospital based, cross sectional, comparative study conducted in 80 patients over a period of 1 year (July 2018 to June 2019) at Institute of Respiratory diseases, SMS Medical College, Jaipur, Rajasthan. Study approval was taken from Ethics committee and Research Review board of SMS Medical College, Jaipur.

INCLUSION CRITERIA

Patients giving consent and in whom endobronchial lesions could be documented were included in the study.

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EXCLUSION CRITERIA

Patients having previous history of severe bleeding in earlier bronchial biopsy, coagulation abnormality, severe cardio-respiratory distress and with haemoglobin < 8gm% were excluded. Patients included in the study were assigned alternately to obtain the EBB by either alligator or cup forceps.

SAMPLE SIZE

Sample size was calculated at 80% study power, 95% confidence interval and α error 0.05 assuming significant of severity of bleeding during endoscopy being 1.1% and 5.7% with alligator and cup forceps respectively.

80 consecutive patients (4 biopsy samples each) with documented endobronchial lesion were included in the study and were subjected to endobronchial biopsy alternatively.

STUDY PROTOCOL

Local anaesthesia was induced using 2% xylocaine as jelly in the nostrils and spray as go technique during bronchoscopy. 1ml (1mg/ml) midazolam was used as needed for sedation. Video assisted bronchoscope (Olympus video bronchoscope BF-1TH190) was used, having working channel size of 2.8mm, outer diameter of 6mm and working length of 600mm. The two EBB forceps used, had same width and length (width – 1.9mm, length – 1150mm) and both were without spokes. Minimum channel size required for forceps was 2.0mm.

During the video assisted bronchoscopic EBB, 6 samples were obtained from each patient and sample sizing and bleeding were noted.

Sample sizing was described as: if sample did not fill the forceps, it would be considered as 'small', if it filled forceps, it was considered as 'medium', and if it was larger than forceps, it would be considered as 'large' sample.

At the end of the procedure, bleeding severity was assessed as: if bleeding did not require any intervention, it was considered as 'mild', if suctioning was required to clear bronchoscopy field, bleeding was considered as 'moderate' and if interventions such use of ice cold saline (CS), topical tranexamic acid (TA), topical adrenaline (Adr), or argon plasma coagulation (APC) were required, it was considered as 'significant'. Also, highest mode of intervention used to control bleeding was noted.

After the procedure, samples were sent for histopathological analysis, and described as: 1) Sample tissue size in millimeters (mm), and were grouped in to 4 categories: maximum size of tissue upto 4mm, between 4 - 6mm, 6 - 8mm and 8 -10mm. 2) Diagnostic or non-diagnostic. In each patient, maximum size of sample was noted (and not of individual tissue).

Quantitative / categorical data was presented as proportion and was analysed using 'chi square test'. Quantitative data was presented as mean and standard deviation.

DATA ANALYSIS

Statistical analysis was performed using 'primer version 6.0' statistical software.

Quantitative / categorical data was presented as proportion and was analysed using 'Chi square test'. Quantitative data was presented as mean and standard deviation and difference in mean was analysed using 'unpaired t test'.

RESULTS

Eighty patients were included in the study with most being males (71, 88.75%). Mean age of the study population was 58.138 ± 10.865 years.

Six samples were obtained from each patient. The differences in demographic, clinical and radiological profiles were non-significant in the 2 groups.

The size of largest piece obtained from 80 patients ranged from small (20, 25%), medium (51, 63.75%) and large (9, 11.25%). With regards to size as per type of forceps, alligator forceps yielded small (6, 15%), medium (27, 67.5%) and large (7, 17.5%) and cup forceps yielded small (14, 35%), medium (24, 60%) and large (2, 5%) (table 1). The number of small samples taken by cup forceps (n = 14) were more than twice the number of those taken by alligator forceps (n = 6) and the difference was found to be statistically significant (p = 0.038). This difference was not significant regarding medium and large samples.

Table 1: Size of largest tissue with respect to forceps blade

Type of biopsy forceps / Size of tissue	Alligator(40) N (%)	Cup (40) N (%)	P value* (LS)
Large (9, 11.25%)	7 (17.5)	2 (5)	0.076 (NS)
Medium (51, 63.75%)	27 (67.5)	24 (60)	0.485 (NS)
Small (20, 25%)	6 (15)	14 (35)	0.038 (S)

*p-value was calculated using chi- square test, p = 0.046 (S).

With respect to tissue size by pathological review, alligator forceps resulted in more samples of tissue size >8mm than cup forceps and the difference was found to be significant (p = 0.011) (table 2).

Table 2: Size of tissue by pathological review.

Type of biopsy forceps / Maximum size of tissue	Alligator (40) N (%)	Cup (40) N (%)	P value* (LS)
Upto 4mm (57, 71.25%)	25 (62.5)	32 (80)	0.083 (NS)
Between 4 - 6mm (12, 15%)	6 (15)	6 (15)	1.000 (NS)
Between 6 - 8mm (5, 6.25%)	3 (7.5)	2 (5)	0.644 (NS)
More than 8mm (6, 7.5%)	6 (15)	0 (0)	0.011 (S)

*p-value was calculated using chi- square test, p = 0.07 (NS).

Severity of bleeding is elaborated in table 3. Highest mode of intervention used to control bleeding, CS + TA combination, was used more times in population of cup forceps, which was found to be statistically significant (p = 0.036). Highest mode of intervention (APC) was used more times in cup forceps population, but it was found to be statistically non-significant.

Table 3: Severity of bleeding

Severity of bleeding	Type of biopsy forceps/Type of intervention	Alligator (40) N (%)	Cup (40) N (%)	P value* (LS)
Mild	No intervention (3, 3.75%)	0 (0)	0 (0)	N/A
Moderate	Suction only (15, 18.75%)	11 (27.5)	7 (17.5)	0.284 (NS)
Significant	CS (11, 13.75%)	7 (17.5)	4 (10)	0.330 (NS)
	CS + TA (29, 36.25%)	10 (25)	19 (47.5)	0.036 (S)
	CS + TA + Adr (16, 20%)	11 (27.5)	5 (12.5)	0.093 (NS)
	CS + TA + Adr + APC (6, 7.5%)	1 (2.5)	5 (12.5)	0.089 (NS)

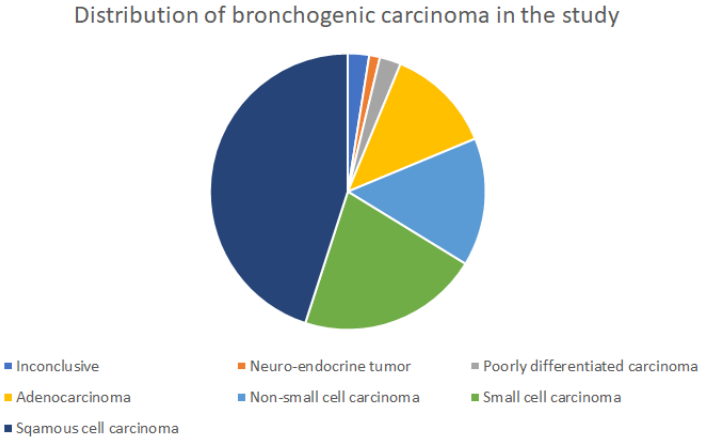
*p-value was calculated using chi- square test, p = 0.092 (NS).

CS = cold saline; TA = tranexamic acid; Adr = adrenaline; APC = argon plasma coagulation.

Diagnostic yield was same for both the forceps (39/40, 97.5%). Pathological diagnosis by each forceps is elaborated in Bar chart. Out of total 80 patients, biopsy with either forceps (total, with alligator and cup forceps, respectively) revealed 1 (1.25%) as neuro-endocrine tumor, 2 (2.5%) as poorly differentiated carcinoma, 10 (12.5%) as adenocarcinoma, 12 (15%) as non-small cell carcinoma, 17 (21.25%) as small cell carcinoma, 36 (45%) as squamous cell carcinoma and 2 (2.5%) were found to be inconclusive.

Table 4: Pathological diagnosis by each forceps

Type of biopsy forceps / Pathology	Alligator(40) N (%)	Cup (40) N (%)
Inconclusive (2, 2.5%)	1 (2.5)	1 (2.5)
Neuro-endocrine tumor (1, 1.25%)	0 (0)	1 (2.5)
Poorly differentiated carcinoma(2,2.5%)	2 (5)	0 (0)
Adenocarcinoma (10, 12.5%)	6 (15)	4 (10)
Non-small cell carcinoma (12, 15%)	6 (15)	6 (15)
Small cell carcinoma (17, 21.25%)	7 (17.5)	10 (25)
Squamous cell carcinoma (36, 45%)	18 (45)	18 (45)



DISCUSSION

With increasing demand of safer and more effective procedure for biopsies of various tissues, our study tries to demonstrate the differences in cup and alligator forceps for EBB and tries to find out, which one is more effective and safe.

In our study, diagnostic yield was found to be 97.5%, and it was same for the two forceps (97.5%). Significantly larger tissue size was obtained with alligator forceps (p = 0.038 – with respect to forceps blade and p = 0.011 – by pathological review), and severity of bleeding was found to be more with cup forceps, but it was found to be statistically non-significant (p = 0.092). Highest mode of intervention to control bleeding during EBB was APC, and it was used more times with cup forceps, but the difference was not statistically significant. However, there was significant difference for the use of CS + TA combination (p = 0.036), favoring alligator forceps.

There have been studies comparing alligator and cup forceps for transbronchial biopsy (TBLB), but there is no previous data available for the two forceps in EBB. Sehgal et al.[3] performed a randomized controlled trial comparing alligator and cup forceps in patients of sarcoidosis.[3] Yield and size of tissue obtained by the two forceps were same, but complications (bleeding and pneumothorax) were more common with cup forceps.[3] Similarly, Jabbardarjani et al.[4] compared the two forceps for TBLB and concluded that biopsy yield and complications (bleeding and pneumothorax) were higher with cup forceps, and tissue size obtained was more with alligator forceps, but the differences were not statistically significant.[4]

During flexible bronchoscopy, endobronchial biopsy is commonly performed to obtain tissue for pathological analysis.[1] Yield of EBB depends on multiple factors, such as, bronchoscopist, central or peripheral lesion, number of biopsy samples taken, type of forcep used to take biopsy.[1] There are multiple types and sizes of forceps available for EBB, but direct comparisons between them have not been performed.[1]

Many complications can occur during and following bronchoscopy. Major complications include death, cardiopulmonary arrest, myocardial infarction, pneumonia, airways obstruction severe enough to require therapy, pulmonary haemorrhage requiring transfusion, seizures and stroke.[2] Minor complications include bleeding in amounts greater than 50ml but not requiring transfusion, vaso-vagal reaction, mild airways obstruction and arrhythmia.[2]

Of the available type of forceps for EBB, we compared cup and alligator forceps, without spikes (same width and length (width – 1.9mm, length – 1150mm) in terms of yield and complications and EBB was performed by same bronchoscopist.

Various methods have been used to quantify bleeding during bronchoscopy in the past. O. Bjortuft et al.[5] collected blood and saline in vacuum suction system. They compared volume and haemoglobin of mixed blood collected (VM and HbM) with haemoglobin of patient (HbP) measured before procedure and blood loss was calculated using formula: VMXHbM/HbP. Blood loss of >20mL was considered significant.[5] In BTS guidelines 2013, severity of bleeding was defined by the need of intervention required to stop bleeding. It was classified as no bleeding - when continuous suctioning is not needed, mild – when continuous suctioning is required, moderate – when biopsied segment is intubated with bronchoscope in a wedge position or with use of cold saline and tranexamic acid, adrenaline is used, severe – when placement of bronchus blocker or catheter, or application of fibrin sealant, resuscitation, blood transfusion, admission to critical care unit is required or death has occurred.[6] In Delphi Consensus Statement From the Nashville Working Group, severity of bleeding was classified according to intervention needed. Grade 1 – suctioning required for <1min, Grade 2 – suctioning required for >1min or wedging of bronchoscope or instillation of cold saline, diluted vasoactive substances or thrombin, Grade 3 – selective intubation with ETT or balloon/bronchial blocker for <20min or premature interruption of procedure, Grade 4 – persistent selective intubation for >20min or new admission to ICU or PRBC transfusion or need for bronchial artery embolization or resuscitation.[7] In our study, severity of bleeding was classified as mild – no intervention required, moderate – only suctioning required, and severe – instillation of cold saline, tranexamic acid, adrenaline or use of APC was required.

There are many methods used to control bleeding during flexible bronchoscopy, most commonly used being cold saline, tranexamic acid and topical adrenaline. S. Badovinac et al. performed a double blind randomized control trial comparing tranexamic acid and adrenaline for controlling iatrogenic bleeding during flexible bronchoscopy, but found no significant difference between effect of tranexamic acid and adrenaline for controlling non-catastrophic iatrogenic endobronchial bleeding, after cold saline failure.[8]

Diagnostic yield with the two forceps (alligator and cup forceps) have been compared in TBLB. Smith et al found diagnostic yield to be 80% and 22.22%, Jabbardarjani et al found yield to be 54.5% and 40.9%, Sehgal et al found 64.3% and 60.6% yield and Almadani et al found yield to be 42.5% and 27.5%, respectively with cup and alligator forceps.[3,4,9,10] In our study, yield in EBB was same with both forceps as 97.5% each.

Limitations of the study: it was a single centre study, with lack of randomization, and architectural preservation of sampled tissue and sizing of every sample were not performed. However, the findings are novel and provide insight into the yield and complication rate for the two types of biopsy forceps commonly used for bronchial biopsies.

CONCLUSION

Using alligator forceps for EBB results in larger tissue size and lesser complication rate, but diagnostic yield is same for the two forceps. However, larger randomized studies are needed to validate the findings.

ABBREVIATIONS

EBB : Endobronchial biopsy
TB : Tuberculosis
CS : Cold saline
TA : Tranexamic acid
Adr : Adrenaline
APC : Argon plasma coagulation
TBLB : Transbronchial lung biopsy

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AVAILABILITY OF DATA AND MATERIALS

Data will be available by emailing at vinayakmangal@gmail.com

AUTHORS CONTRIBUTIONS

Author 1: participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing and editing.

Author 2: participated in the investigation, conceptualization, writing review, data collection and editing.

Author 3: participated in data collection, writing, reviewing and editing.

Author 4: participated in data collection, data analysis, writing, reviewing and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The research adhered to the ethical principles outlined in the Declaration of Helsinki (2013). Approval for the study protocol was granted by Ethics committee and Research Review board of SMS Medical college, Jaipur. Electronic signatures were obtained as informed consent from all individual participants involved in the study. Every procedure conducted during the study complied with the standards of Ethics committee and Research Review board of SMS Medical college and aligned with the principles set forth in the 1964 Helsinki Declaration, along with its subsequent amendments.

COMPETING INTEREST

The authors declare that they have no competing interests.

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Original Article

Reduction in Central Line Associated Blood Stream Infection (CLABSI) in NICU: A Quality Improvement Study

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ABSTRACT

Introduction: Central Line Associated Blood Stream Infections (CLABSI) are common in extremely premature and low birth weight infants.

Aims And Objectives: The aim of this study was to use care bundle approach to reduce the CLABSI rates amongst neonates admitted in NICU by 50% over a 6-month period and to sustain this over the next 2 years.

MATERIAL AND METHODS

A Quality improvement study using WHO Point of care Quality Improvement Model (POCQI) using PDSA cycles approach (Plan-Do-Study-Act) was initiated in Feb'2020. The study was carried out in a tertiary level NICU in Jaipur, India over a period of 2.5 year. The QI study was divided into various phases which included baseline surveillance, PDSA cycles and period of sustainability.

Results: CLABSI rate during baseline surveillance period (3 months) was 26.5 episodes per 1000 lines days. During PDSA 1 (3 months), it reduced to 15.3 episodes per 1000 lines days. In PDSA 2 (3 months) there was further reduction in CLABSI rate to 9.56 episodes per 1000-line days. Both interventions of PDSA 1 and 2 were continued in the sustainability period. Over next 2 years, CLABSI rate was 7.27 per 1000-line days. CLABSI rate was also audited every 6 months during sustainability period and it was 6.07, 3.5, 9.5 and 10.7 per 1000-line days respectively. We were able to sustain more than 50% reduction in CLABSI rates in our QI project.

Conclusion: Monitoring of the CLABSI rates and implementation of CLABSI bundle is of paramount importance in sick newborn care.

INTRODUCTION

Health care associated infections (HAI) or nosocomial sepsis are a major concern for preterm and sick neonates requiring prolonged hospitalization. Advances in neonatal care has led to a better survival of smaller and sicker newborns which has contributed to the increased risk of HAI. Such nosocomial infections not only jeopardize the survival and neurodevelopmental outcomes in these babies but also increases the cost of care significantly. [1]

Establishing and maintaining secure vascular access is important specifically for sick and preterm babies. Central Venous Catheters (CVC) commonly used in the NICU include Peripherally Inserted Central Venous Catheters (PICC), Umbilical Venous Catheters (UVC) and Umbilical Arterial Catheters (UAC). These venous catheters allow reliable administration of fluid, total parenteral nutrition and medications while the arterial lines enable accurate and sustained blood pressure monitoring along with blood sampling. Central lines although essential, pose a risk of Central Line Associated Blood Stream Infections (CLABSI), particularly in extremely premature and low birth weight infants who exhibit poor skin integrity, immature immune system and require prolonged use of these central lines. [2]

The United States Centre for Disease Control and Prevention, CDC, defines CLABSI as "a primary blood stream infection in a patient that had a central line within the 48-hour period before the development of the blood stream infection, and is not related to an infection at another site". The incidence of CLABSI varies between NICUs, ranging between 1.6 and 15 per 1,000 central line days. In Lower middle-income countries, this rate can range between 35 to 64 CLABSI episodes per 1000 central line days. [3]

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Prevention of CLABSI is crucial to the reduction of associated morbidity, mortality and financial burden. Evidence based care of central lines has resulted in decreased CLABSI rates with the use of healthcare intervention "bundles". Despite the evidence for care bundles in preventing infections, implementation is a challenge requiring training, commitment and constant vigilance to maintain compliance. Hence, quality improvement (QI) principles are needed to bridge the know-do gap. [4]

A QI project was designed to address accurate measurement of the problem, implement steps to reduce CLABSI episodes and sustain the results achieved. The aim of this study was to use care bundle approach to reduce the CLABSI rates amongst neonates admitted to NICU by 50% over a 6-month period and to sustain this over the next 12 months.

METHODOLOGY

A Quality improvement study using WHO Point of care Quality Improvement Model (POCQI) using PDSA cycles approach (Plan-Do-Study-Act) was initiated in Feb'2020. The study was carried out in a tertiary care level 3 NICU in a private hospital in Jaipur. Ethics committee clearance was taken.

A QI team was formed involving doctors (Neonatologist and senior registrars), NICU nurses, infection control nurse and members from administration at the beginning of the study. A Root cause analysis was done to identify various causes of CLABSI, which were contributing to higher CLABSI rates: non-compliance with aseptic technique, inconsistent utilization of the aseptic dedicated kits, poor hand hygiene, poor adherence with line hygiene during disconnection and TPN connection, over-use and prolonged unchecked use of central lines. (Fig 1)

The QI study was divided into various phases which included baseline surveillance, PDSA cycles and period of sustainability.

Baseline data: (Feb-April 2020)	PDSA 1 (May-July 2020)
• Baseline information was recorded • Total central line days were recorded in an Excel sheet • Episodes of CLABSI were recorded as per blood culture reports	• Introduced CLABSI forms which includes bundles and compliance tables **(table 1 and 2)** • Education of nurses was done (Bedside teaching and training) • Daily CLABSI rounds with nurses and suggesting plan of care.
	• Assessing compliance based on google forms • Regular classes on infection control and TPN preparation and connection • Hand Hygiene reinforcement Availability of standard insertion kits (autoclaved)

PDSA 2 (August 2020-October 2020)	Period of Sustainability (November 2020 to October 2022)
Direct supervision of neonatal consultants while attaching the TPN and its preparation Regular reinforcement and motivation Regular training session along with continued intervention from PDSA 1	PDSA 1 and PDSA 2 intervention continued along with regular audits every 6 months.

Figure 1: Fish bone diagram for root-cause analysis

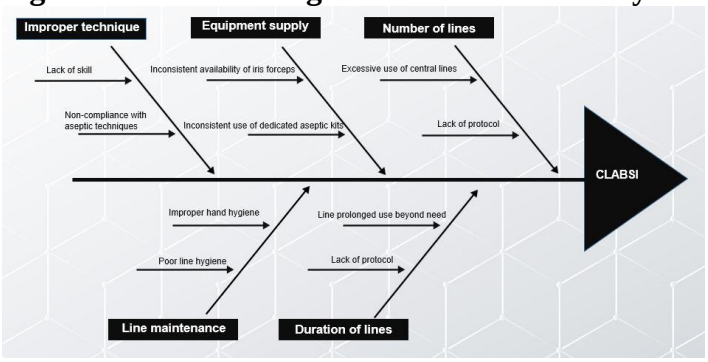

Table 1: Central line: Insertion bundle

Hand wash with 4 % chlorhexidine for 2 minutes	Clean the site with 2 % chlorhexidine in term babies and 0.5 % in preterm babies
Maximal barrier precaution: wear cap, mask, gown and use plastic sheets as drape	Secure the catheter with steristrips and apply a sterile transparent dressing
Wear double non powdered non latex gloves. Remove outer glove before line handling	Run heparinised saline (1 ml = 1 unit) to prevent blockage of line after insertion.

Table 2: Central line: Maintenance bundle

Daily review for need of line. Remove line if enteral feed >120 ml/kg/day	Hand wash before line handling. After hand wash, wear protecto (sterile) gloves
Check for dressing integrity and site cleanliness every shift. Change dressing only if significant soiling with blood. In case of peel off, augment with new tegaderm.	Assemble and connect infusion tubing using sterile technique. Minimal disconnection of long line.

Use "closed" systems for infusion (Q syte). Change Q syte every 4 days. Attach during TPN preparation.	Scrub Qsyte with alcohol swab for 15 sec prior to entry. Dry for 15 sec
UVC should be replaced with PIC line in 5-7 days if longer duration of access is needed	UVC can be used for maximum 10 days. UAC can be used for 7 days PIC line can be used for 4 weeks.
Change TPN fluid every 48 hrly and lipid every 24 hourly	Use of laminar flow for TPN preparation.

RESULTS

The study has been successfully completed over a duration of 2.5 year. The PDSA cycles were implemented as planned and there was good response from the NICU team. We were able to maintain the record by performing daily checks and entry into the excel sheet. At the end of the month, central lines days were recorded and saved along with number of infection and isolated organism.

The central lines days during the four phases of PDSA cycles were 301, 195, 205 and 825 days respectively. Similarly, the recorded number of CLABSI episodes were 8, 3, 2 and 6 respectively. **(Fig 2)** Common organism isolated were Klebsiella (8), Coagulase negative staphylococcus (4), Acinetobacter (3), Enterobacter (2) and one each of staphylococcus (MRSA) and E. Coli. Multidrug resistant Klebsiella is the most common pathogenic organism for CLABSI in our NICU.

Out of the total 19 episodes of CLABSI in the last 2.5 year, 15 was associated with UVC while 4 was associated with PIC line. CLABSI rate during baseline surveillance period was 26.5 episodes per 1000 lines days. During PDSA 1, it reduced to 15.3 episodes per 1000 lines days. In PDSA 2 of 3 months, there was further reduction in CLABSI rate to 9.56 episodes per 1000-line days. Both interventions of PDSA 1 and 2 were continued in the sustainability period. Over next 2 years, CLABSI rate was 7.27 per 1000-line days. **(Fig 3)** CLABSI rate was also audited every 6 months during sustainability period and it was 6.07, 3.5, 9.5 and 10.7 per 1000-line days respectively. We were able to sustain more than 50% reduction in CLABSI rates in our QI project. Central line infection was more common with UVC than PIC Line. Compliance of insertion and maintenance bundle assessed as per google forms was more than 95%.

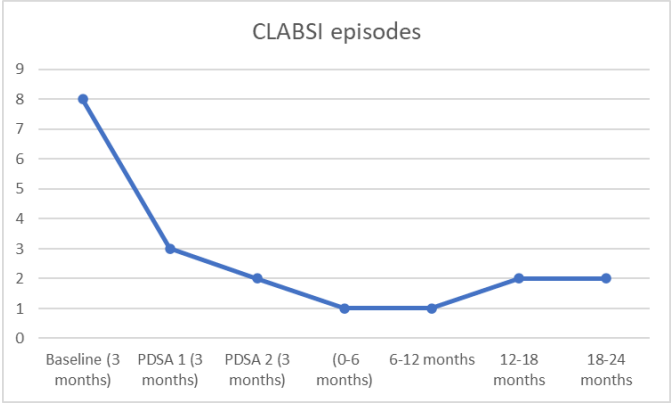

Figure 2: CLABSI episodes in various phases of study duration

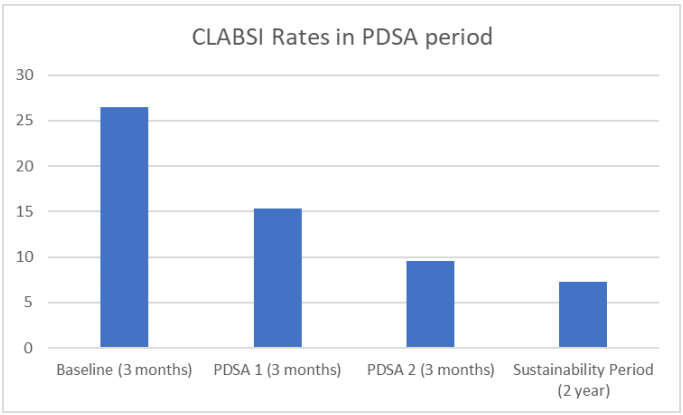

Figure 3: CLABSI rates during various phases of PDSA Cycles

Discussion

This quality improvement (QI) study demonstrated a substantial and sustained reduction in CLABSI rates in a level 3 NICU through structured, phased implementation of central line insertion and maintenance bundles. By utilizing the WHO Point of Care Quality Improvement (POCQI) methodology and the Plan-Do-Study-Act (PDSA) cycles, the intervention successfully decreased CLABSI rates by more than 70%, from 26.5 to 7.27 per 1,000 central line days over a two-year period. Importantly, this reduction was maintained during the sustainability phase, highlighting the feasibility of long-term implementation of such interventions in similar neonatal care settings.

Our findings are consistent with previous QI initiatives that have demonstrated the effectiveness of care bundle implementation in reducing healthcare-associated infections. Balla et al. reported an 89% reduction in CLABSI rates using similar QI strategies in a tertiary NICU in India, emphasizing the impact of reinforcing hand hygiene, standardizing line care, and conducting regular audits and feedback sessions to

drive behavioural change among healthcare providers [5]. The present study supports this by showing a direct correlation between improved bundle compliance (exceeding 95%) and a marked decline in CLABSI incidence.

A notable strength of our project was the integration of multiple stakeholders—including neonatologists, nurses, infection control staff, and administrators—into the QI team. This multidisciplinary approach allowed for comprehensive identification of root causes, such as inconsistent hand hygiene, improper line handling techniques, and prolonged line retention, as visualized in the fishbone diagram. The incorporation of real-time data tracking using Excel sheets and Google Forms for compliance assessment enabled continuous process monitoring and timely course correction.

The microbiological profile of CLABSI in our unit, dominated by multidrug-resistant Klebsiella species, mirrors national trends where gram-negative pathogens continue to pose a major challenge in NICUs [6,7]. Most CLABSI episodes were associated with umbilical venous catheters (UVCs), reinforcing the need for timely transition to peripherally inserted central catheters (PICCs) as per protocol. This aligns with global recommendations advocating for the limited duration of UVC use and early removal of central lines when no longer necessary [8].

A key factor in the success of our interventions was the phased implementation of PDSA cycles. Each cycle was focused, feasible, and aligned with staff capacity and institutional resources. The early emphasis on education, hand hygiene training, and introduction of standard insertion kits laid a foundation for behavior change, which was reinforced by direct supervision and routine audits during the sustainability phase. Feedback loops through data visualization and periodic team reviews were instrumental in maintaining staff motivation and adherence to protocols—critical elements also identified in other successful QI projects [9.10].

Despite the encouraging outcomes, this study has limitations. Being a single-center study, its generalizability may be limited. Moreover, although compliance was high, the possibility of reporting bias cannot be excluded due to self-reported data on bundle adherence. Additionally, this study did not quantify the impact on other patient-centered outcomes such as length of stay, mortality, or cost-effectiveness, which could provide a more comprehensive evaluation of the intervention's benefits. Also, the impact of COVID 19 pandemic during the study period could have affected the NICU practices during the PDSA cycle phase and surveillance period.

Nevertheless, our results affirm that even in resource-constrained settings, simple, evidence-based interventions—when implemented with strategic planning and team involvement—can lead to meaningful reductions in CLABSI rates. Continuous surveillance, regular staff training, and reinforcement of infection control practices are essential to sustain these gains.

Future studies may explore the integration of automated surveillance tools, investigate the role of antimicrobial stewardship in conjunction with CLABSI prevention, and assess patient outcomes more holistically.

Conclusion

Our QI project was successful in decreasing the incidence of CLABSI in our unit. PDSA cycles were implemented in a phased manner. This helped the team to understand the interventions and were able to implement it and also sustained over a period of time. Regular audits and surveillance instilled confidence in the team and also motivated for better performance. This study will pave the way for other QI studies in the unit which will help in improving the quality of neonatal care in our unit along with improved outcomes.

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Availability of data and materials

Data will be available by emailing drvarun1983@gmail.com

Authors' Contributions

- Author1: participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing, also corresponding author.
- Author 2: participated in the investigation, conceptualization, writing, review, data collection, and editing.
- Author3: participated in data collection, writing, reviewing, and editing.
- Author 4: participated in data collection, writing, reviewing, and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

Ethics approval and consent to participate

The research adhered to the ethical principles outlined in the Declaration of Helsinki (2013). Approval for the study protocol was granted by the Institutional Ethics Committee, in the year 2020, month of January. Electronic signatures were obtained as informed consent from all individual participants involved in the study. Every procedure conducted during the study complied with the standards of Institutional Ethics Committee and aligned with the principles set forth in the 1964 Helsinki Declaration, along with its subsequent amendments.

Competing Interest

The authors declare that they have no competing interests.

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Original Article

Prescription Pattern of Chemotherapeutic Agents in patients with Breast Cancer in a Government Tertiary Care Teaching Hospital - A Prospective Observational Study

Omprakash Choudhary*, Monica Jain, Jaya Sharma*****

Abstract

Background: Breast cancer is a multi-factorial disease, comprises of a group of complex and heterogeneous diseases that evolves due to uncontrolled differentiation, cellular growth, and the loss of normal programmed cell death. This study specifically aimed to evaluate the prescribing patterns of chemotherapeutic agents among breast cancer patients in a tertiary care hospital.

Methods: This prospective, observational cross-sectional study was done from February 2023 to February 2024 at the Department of Medical Oncology at SMS Medical College & Hospitals, Jaipur, focusing on inpatients diagnosed with breast cancer. A total of 100 patients were randomly selected on a first-come basis. **Results:** Most patients (67%) were aged 41-60 years, with a mean age of 49.7 ± 9.93 years. Right-sided breast involvement was predominant, observed in 90% of patients (90 cases), while left-sided involvement was noted in 10% of patients (10 cases). Monotherapy was used by 56% of patients, with Trastuzumab being the most common drug (27%). The majority of patients (84%) adhered to standard treatment guidelines, while 16% did not follow these recommendations. Febrile neutropenia was the most common interaction, reported in 23 patients (23%). Toxicity due to immunosuppressive effects was noted in 22 patients (22%), while increased doxorubicin toxicity via CYP3A4 metabolism and cyclophosphamide toxicity by an unspecified mechanism were observed in 13 patients (13%) each. **Conclusion:** Early detection through widespread education and preventive measures could ultimately improve survival rates and lessen the burden of breast cancer in India and other resource-limited settings.

Keywords: Breast cancer, Drug prescription pattern, Neoadjuvant chemotherapy drugs, Adjuvant chemotherapy drugs, Anticancer drugs.

Introduction

Breast cancer accounted for approximately 25% of all cancers among women in 2012, with 1.67 million new cases diagnosed and around 70,218 women succumbing to the disease (a mortality rate of 21.5% of all cancer cases). As a result, breast cancer stands as the primary cause of death in women affected by cancer, boasting a mortality rate of 12.7 per lakh population.[1] At present, the prevalence of breast cancer in India stands at 23 cases per 100,000 women. Over the years, the incidence of breast cancer has surged in India, with as many as 100,000 new cases being identified annually. Notably, in developing countries, older women are at a higher risk of developing breast cancer compared to their younger counterparts.[2]

The management of breast cancer involves a combination of non-drug therapies, medication-based treatments, and surgical procedures. The primary modalities employed in breast cancer treatment are chemotherapy, hormonal therapy, immunotherapy, radiation therapy, and surgery. The selection of a particular therapeutic approach is contingent on factors such as patient characteristics, tumor attributes, and treatment considerations. Different types of chemotherapy—such as adjuvant, neoadjuvant, and palliative—are utilized in treatment. Unlike historical practices where cancers were treated with a single drug, contemporary strategies involve the use of drug combinations to address cancer cell heterogeneity and counter the development of drug-resistant cells, aiming to target the entire tumor cell population.[3]

The pharmacological aspect of management involves the use of anticancer drugs such as 5-fluorouracil, epirubicin, doxorubicin, cyclophosphamide, docetaxel/ paclitaxel, and carboplatin.[4] Chemotherapy is administered to patients in cycles, with each cycle lasting for 2 to 3 weeks. Adjuvant and neo-adjuvant chemotherapy typically spans for a total duration of 3 to 6 months, contingent on the specific drugs employed. Non-pharmacological treatments involve managing risk factors such as obesity, dietary choices, alcohol consumption, low physical activity, and providing guidance on lifestyle modifications. Additionally, patients are advised to avoid exposure to ionizing radiation and environmental pollutants.[5]

Chemotherapy for breast cancer is known to elicit various adverse drug effects, including hair loss, nail

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changes, mouth sores, loss of appetite or weight changes. Specific side effects associated with certain drugs include hemorrhagic cystitis with cyclophosphamide, peripheral neuropathy and neutropenia with Paclitaxel/docetaxel, oto-toxicity and nephrotoxicity with carboplatin, and stomatitis and mucositis with doxorubicin.[6]

The assessment of prescription patterns is a vital component of drug utilization studies. Assessing prescribing patterns for anticancer drugs is essential due to the availability of various regimens, variable response rates with different drugs, and the intolerability of combination regimens. Drug utilization studies offer valuable tools to evaluate the appropriateness of therapy, identify areas for improvement, and enhance medical care in terms of rationality, cost-effectiveness, and standard quality.[7]

By evaluating and comparing prevailing patterns with established standards, steps can be taken to optimize anticancer therapy, aiming for improved efficacy and minimal toxicity. The study's objective is to analyze the clinical profile, prescription patterns, and adverse drug reactions associated with breast cancer.

Methods

This prospective, observational, study was carried out in Department of Medical Oncology of a tertiary care teaching hospital for a period of one year starting from February 2023 to February 2024 after approval from institutional ethics committee. Women diagnosed with breast cancer with a breast carcinoma staging up to stage III and attending medical oncology department for chemotherapy, aged 18-60 years of age, who had underwent at least one cycle of chemotherapy were included in the study. Out-door patients with a diagnosis of breast cancer and Pregnant and lactating women with a diagnosis of breast cancer were excluded from the study.

Those meeting the selection criteria were briefed about the study and written informed consent was obtained from those willing to participate. Their prescriptions were analyzed and the following data was recorded: demographic characteristics, diagnosis, number of drugs prescribed, route of administration, dosing frequency, duration, prescription by generic/ brand name. The data was collected, compiled in MS-Excel and analysed for counts and percentages. The mean and standard deviation were computed for continuous variables.

Sample size:

Sample size was calculated at 95% confidence level & α- error of 0.05 assuming drug utilization of anti-cancer drugs at the time of discharge from hospital among patients of breast cancer at an absolute allowable error of 5%. The required sample size was 100 to allow 10% allowable error.

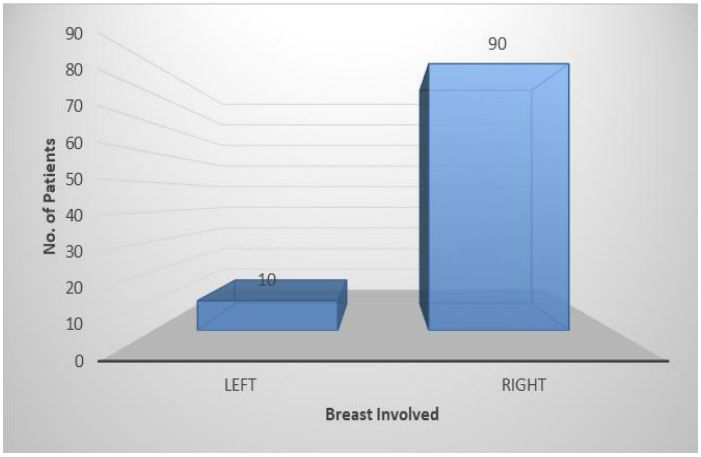
Results

Table 1 shows the general characteristics of study patients. In this study, the age distribution of patients showed that the majority (67%) were in the 41-60 age group (n=67), followed by 19% in the 20-40 age group (n=19), and 14% were over 60 years (n=14). The overall mean age was 49.7 ± 9.93 years.

Age Distribution (in years)	No. of Patients	Percentage
20-40	19	19
41-60	67	67
>60	14	14
Total	100	100
Mean±SD	49.7±9.93	

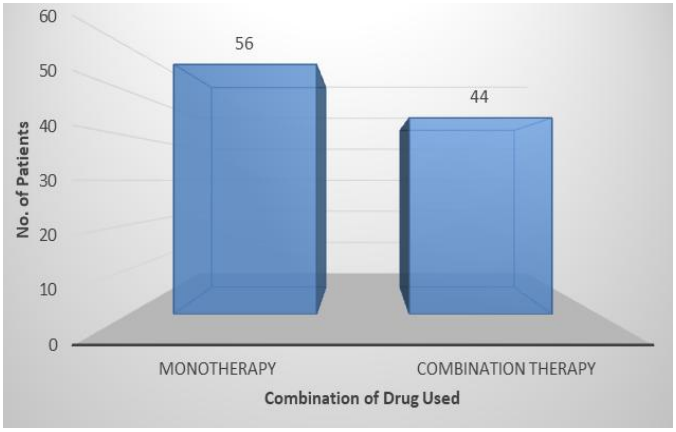
Table 1: Distribution of cases according to Age.

Graph 1 indicates the distribution of breast involvement among patients. The right breast was affected in 90 patients, comprising 90% of the cases, while the left breast was involved in 10 patients, representing 10% of cases.



Graph 1: Distribution of cases according to site.

In the study, the drug usage among patients was categorized as follows: 56% (n=56) were on monotherapy, while 44% (n=44) received combination therapy. (Graph 2)

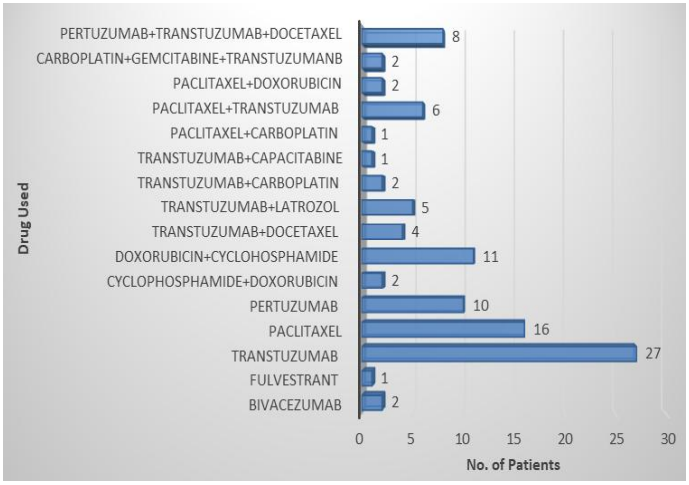


Graph 2. Combination of Drugs used.

In the study, the distribution of drug usage among patients was as follows: Trastuzumab was the most commonly used drug, accounting for 27% (n=27) of patients, followed by Paclitaxel at 16% (n=16) and Pertuzumab at 10% (n=10). Other drugs included Doxorubicin+Cyclophosphamide (11%, n=11), and Pertuzumab+Trastuzumab+Docetaxel (8%, n=8). The remaining medications had lower usage rates, including Trastuzumab+Docetaxel (4%, n=4), and various combinations like Paclitaxel+Trastuzumab (6%, n=6). Overall, monotherapy was noted in 2% (n=2) for Bivacezumab and Cyclophosphamide+ Doxorubicin, with additional combinations used among patients, reflecting a diverse treatment approach. (Table 2, Graph 3)

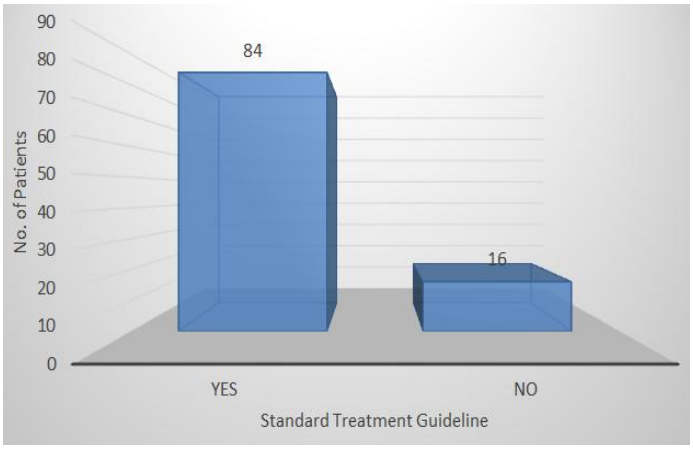
Drug Used	No. of Patients	Percentage
Bivacezumab	2	2
Fulvestrant	1	1
Trastuzumab	27	27
Paclitaxel	16	16
Pertuzumab	10	10
Cyclophosphamide+Doxorubicin	2	2
Doxorubicin+Cyclohosphamide	11	11
Trastuzumab+Docetaxel	4	4
Trastuzumab+Latrozol	5	5
Trastuzumab+Carboplatin	2	2
Trastuzumab+Capacitabine	1	1
Paclitaxel+Carboplatin	1	1
Paclitaxel+Trastuzumab	6	6
Paclitaxel+Doxorubicin	2	2
Carboplatin+Gemcitabine+ Transtuzumanb	2	2
Pertuzumab+Trastuzumab+ Docetaxel	8	8
Total	100	100

Table 2: Distribution of cases according to drug used.



Graph 3: Distribution of cases according to drug used.

Out of the total population, 84 patients (84%) received treatment in accordance with standard guidelines, while 16 patients (16%) did not follow these guidelines.(Graph 4)



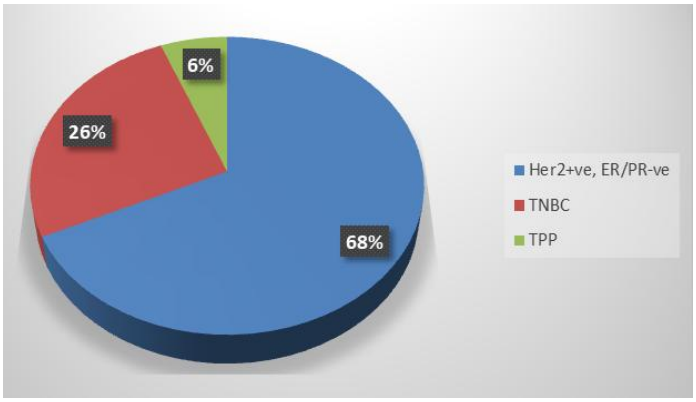
Graph 4: Distribution of cases according to Standard Treatment Guideline

The table 3 summarizes data on drug-drug interactions observed in a patient population. Febrile neutropenia was the most frequently reported interaction, affecting 23 patients, representing 23% of cases. Drug interactions resulting in an increase in the toxicity of other drugs due to immunosuppressive effects were observed in 22 patients (22%). Increased effect of doxorubicin, linked to alterations in CYP3A4 metabolism, was noted in 13 patients (13%), as was the increased toxicity of cyclophosphamide via an unspecified mechanism. A smaller number of interactions included paclitaxel increasing doxorubicin levels by reducing renal clearance (2 patients, 2%), risk of cardiotoxicity (2 patients, 2%), and risk of infection (23 patients, 23%). Lastly, a single case (1%) involved a general increase in drug toxicity.

Drug-Drug Interaction	No. of Patients	Percentage
Febrile Neutropenia	23	23
Increase Toxicity of Other Drug	1	1
Increase Toxicity of Other Drug by Immunosuppressive Effects	22	22
Increased Effect of Doxorubicin by affecting CYP3A4 Metabolism	13	13
Increased Toxicity of Cyclophosphamide by unspecified mechanism	13	13
Paclitaxel increases levels of Doxorubicin by decreasing renal clearance	2	2
Risk of Cardiotoxicity	2	2
Risk of Infection	23	23

Table 3: Distribution of cases according to Drug-Drug Interaction

Among the 100 patients, 55% received adjuvant therapy, while 45% underwent neoadjuvant therapy. Among the 100 patients, 68% had Her2-positive and ER/PR-negative profiles, 26% had triple-negative breast cancer (TNBC), and 6% had a triple-positive profile (TPP).(Graph 5)



Graph 5: Molecular profile of breast cancer in patients

Discussion

Breast cancer (BC) remains a significant health concern in developing nations. Chemotherapy has been widely implemented to reduce BC-related morbidity, lower recurrence rates, and improve patient survival. However, its widespread application has led to issues such as increased resistance to treatment, avoidable adverse reactions, and suboptimal patient management.[8] Breast cancer is the leading cancer among women in both developed and developing regions. In China, Luminal B (HER2-negative) breast cancer is predominant, particularly among younger women under 40 years of age.[9]

DEMOGRAPHIC DATA

In this study, the age distribution revealed that a majority (67%) of patients were in the 41-60 age range (n=67), with 19% in the 20-40 age range (n=19), and 14% above 60 years (n=14). The overall mean age was 49.7 ± 9.93 years.

Similarly, **Wahlang J B et al.[10]** found a mean age of 48.71 ± 15.94 years in their study population. In contrast, **Mathur R et al.[11]** noted that the largest portion of their participants—38 patients, or 30% of the total—were within the 51-60 age group. Additionally, 21 patients were under 41 years, and 19 were over 70.

This finding aligns with similar studies by **Rout A et al.** and **Prasad A et al.[12,13]**, which observed that the 51-60 age group was predominant, closely followed by the 61-70 age group, which accounted for 21% of ADRs, and the 41-50 age group at 17% of ADRs. Other studies, including those by **Chakraborty et al.** and **Chopra et al.[14,7],** have also shown that ADR occurrences were notably higher among patients in the 41-50 age bracket.

COMBINATION OF DRUG USED

In this study, drug usage among patients was divided into monotherapy and combination therapy, with 56% (n=56) of patients on monotherapy and 44% (n=44) receiving combination therapy.

In a similar study, **Sah R et al.[9]** analyzed drug therapies among 10 patients, also grouping them into monotherapy and combination therapy. In the monotherapy group, Trastuzumab was the most common drug, used by 4 patients (50%), followed by Paclitaxel and Zoledronic Acid, each administered to 1 patient (10%). In the combination therapy group, two specific regimens were observed: Cyclophosphamide + Docetaxel and Cyclophosphamide + Epirubicin, each given to 2 patients (20%).

DRUG USED

In this study, Trastuzumab emerged as the most frequently used drug, prescribed to 27% (n=27) of patients, followed by Paclitaxel at 16% (n=16) and Pertuzumab at 10% (n=10). Additionally, Doxorubicin + Cyclophosphamide was used in 11% (n=11) of cases, and Pertuzumab + Trastuzumab + Docetaxel in 8% (n=8). Lower usage rates were noted for Trastuzumab + Docetaxel (4%, n=4), as well as combinations like Paclitaxel + Trastuzumab (6%, n=6). Monotherapy was less common, seen in only 2% (n=2) for drugs like Bevacizumab and Cyclophosphamide + Doxorubicin, highlighting a diverse treatment strategy.

Wahlang J B et al.[10] reported a similar pattern, with cisplatin, cyclophosphamide, paclitaxel, and 5-FU frequently used in chemotherapy regimens for cancers prevalent in their region, including lung, esophageal, and lymphatic cancers. Other drugs like carboplatin, oxaliplatin, docetaxel, and doxorubicin were prominent in treating cancers of the breast, cervix, ovary, uterus, stomach, rectum, and colon.

In contrast, **Mathur R et al.[11]** found that the platinum coordination complex, particularly carboplatin, was the most common class of anti-cancer drugs used, followed by cisplatin. These findings were consistent with studies by **Guduru H et al.,[15]** where carboplatin and paclitaxel were also widely used.

This outcome diverged from findings in the **Chopra study**, which observed cisplatin as the primary drug prescribed.[7]

STANDARD TREATMENT GUIDELINE In the present study out of the total population, 84 patients (84%) received treatment according to standard guidelines, while 16 patients (16%) did not.

DRUG-DRUG INTERACTION

In the present study, febrile neutropenia was the most frequently reported interaction, affecting 23 patients (23% of cases). Drug interactions that increased the

toxicity of other drugs due to immunosuppressive effects were observed in 22 patients (22%). An increased effect of doxorubicin, associated with alterations in CYP3A4 metabolism, was documented in 13 patients (13%), as was the increased toxicity of cyclophosphamide through an unspecified mechanism. Fewer interactions included paclitaxel elevating doxorubicin levels by reducing renal clearance (2 patients, 2%), the risk of cardiotoxicity (2 patients, 2%), and the risk of infection (23 patients, 23%). A general increase in drug toxicity was noted in one case (1%).

Conclusion

Breast cancer poses a significant health risk, particularly in developing countries like India, where awareness and access to healthcare resources can be limited. This study focused on breast cancer patients in Jaipur, Rajasthan, India, aiming to analyze the patterns of breast carcinoma and the therapeutic regimens administered. Identifying these patterns can also highlight areas that need improvement in healthcare delivery and patient management. Additionally, raising awareness about breast cancer screening and available treatment options among the general population could play a pivotal role in reducing disease-related mortality. Early detection through widespread education and preventive measures could ultimately improve survival rates and lessen the burden of breast cancer in India and other resource-limited settings.

Abbreviations

BC : Breast Cancer

ER/PR : Estrogen Receptor/Progesterone Receptor

HER2 : Human Epidermal Growth Factor Receptor 2

TNBC : Triple-Negative Breast Cancer

TPP : Triple-Positive Profile

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Availability of data and materials

Data will be available by emailing jayasharma155@gmail.com

Authors' Contributions

- Author 1: Participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing.

- Author 2: Participated in the investigation, conceptualization, writing, review, data collection, and editing.

- Author 3*: Corresponding author participated in data collection, writing, reviewing, and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

Ethics approval and consent to participate

The research adhered to the ethical principles outlined in the Declaration of Helsinki (2013). Approval for the study protocol was granted by the Office of the Ethics Committee, SMS Medical College & Attached Hospital, Jaipur, with a decision number of 355/MC/EC/2023 in 2023. Electronic signatures were obtained as informed consent from all individual participants involved in the study. Every procedure conducted during the study complied with the standards of Ethics Committee and aligned with the principles set forth in the 1964 Helsinki Declaration, along with its subsequent amendments.

Competing Interest

The authors declare that they have no competing interests.

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Original Article

Evaluation of the Knowledge of Phase-II Undergraduate Medical Students on Substance Abuse and its Management

Ishita Agarwal*, Kopal Sharma, Monica Jain***, Kavita Bhakar*, Muskan Jain******

ABSTRACT

Background: Substance abuse continues to pose a significant challenge to global health with detrimental socioeconomic repercussions. Enhanced educational strategies aim to develop more competent healthcare professionals along with a well-informed and responsible society. The purpose of this study was to evaluate the knowledge acquired by the phase-II medical undergraduates on substance abuse and its management, following completion of the corresponding learning session. **Methods:** A cross-sectional study was conducted using a questionnaire, distributed via Google forms, among the undergraduate students. Responses were analyzed to identify their knowledge levels and therefore, perceived learning gain. **Results:** Majority of the participants (73.99%) had good knowledge about substance abuse and de-addiction. 90.13% of the total participants correctly identified clinical cases of opioid toxicity, requiring suitable management. Approximately 85% of the total participants understood the mechanisms underlying alcohol and nicotine abuse. **Conclusion:** The findings of this study conclude that majority of the participating students had good knowledge about substance abuse and de-addiction. There is an imperative need for structured and specialized training in substance abuse and its management to ensure timely and adequate interventions, thereby reducing the morbidity and mortality associated with it.

Keywords: Substance abuse; De-addiction; Medical students; Competency.

INTRODUCTION

Drug addiction is a chronic, relapsing disorder where a person compulsively seeks and takes a drug despite its serious negative consequences on his/her health.[1] Addictive substances induce euphoria and help relieve distress. However, they often lead to the development of tolerance, physical dependence and craving.[2] Commonly abused substances include depressants like opioids, ethanol and benzodiazepines, stimulants like cocaine, amphetamine and related compounds and hallucinogens like cannabinoid receptor agonists.[3]

Due to the contribution of biological, sociocultural, economic as well as psychological factors, treatment of substance abuse involves variety of treatment approaches. Methadone maintenance for treatment of opiate addicts, detoxification programs, along with establishment of therapeutic communities have provided consistent results.[4] Outpatient drug-free programs, focusing on relapse prevention, have also been established (National Association of State Alcohol and Drug Abuse Directors [NASADAD] 1988).[4]

Medical education has changed from being a teacher-centered process to a learner-centered process (thereby focusing on what the students learn rather than what the educator teaches). This encourages the students to become competent and reflective practitioners.[5] Given the increased demand for substance abuse treatment, there is an urgent need for enhanced education on this topic in the preclinical years of medical school, along with improved training during the subsequent clinical years.[6]

The second-year MBBS curriculum, as stated by the NMC, includes the topics of substance abuse, dependence and de-addiction under Pharmacology, Forensic Medicine and Toxicology, and General Medicine.[7] So, we planned to carry out this study with phase-II undergraduate medical students to evaluate the knowledge acquired by them, after their learning session on substances of abuse and their management.

METHODS

Study design: This cross-sectional, questionnaire-based study was conducted among the phase-II medical undergraduate students following a one-hour learning session on substance abuse and de-addiction, with the aim of evaluating the knowledge gained from the session. The students were explained the aim and purpose behind the study and the participation in the study was voluntary. The anonymity of each student was ensured.

Sample Size and Sampling Technique: A total of 250 students were approached using convenience sampling. Of these, 223 completed the questionnaire, yielding a response rate of 89.2%.

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Study tool: A structured, pre-validated and self-administered closed ended questionnaire was developed to assess perceived learning gain. It included 15 multiple choice questions, developed in English, evaluating students' understanding of the pharmacology of substances of abuse and their respective de-addiction. The content validity was ensured through subject expert in Pharmacology.

At the end of the learning session of one hour, the questionnaire was shared online among the participating students, using Google Forms. The link of the form was sent to the students via WhatsApp platform.

After completion of the questionnaire, answers with detailed explanations were provided to the respective questions, to increase awareness among the participants.

Data analysis: The collected data was entered in MS Excel version 20 and analyzed using descriptive statistics. The items of the questionnaire were scored as 0-5 (poor knowledge), 6-10 (fair knowledge) and 11-15 (good knowledge).

RESULTS

A total of 223 students completed the questionnaire, giving the response rate of 89.2%. Out of the 223 participants, 64.12% were males and 35.87% were females, as shown in Figure 1. Table 1 presents the questionnaire items along with the corresponding percentage of participants with correct responses. Figure 2 illustrates the distribution of participants based on the percentage of correct answers. Overall, 73.99% of the students had good knowledge about substances of abuse and their management while 28.45% and 18.69% had moderate and poor knowledge respectively, as shown in Table 2.

Figure 1: Distribution of the participants according to their gender-

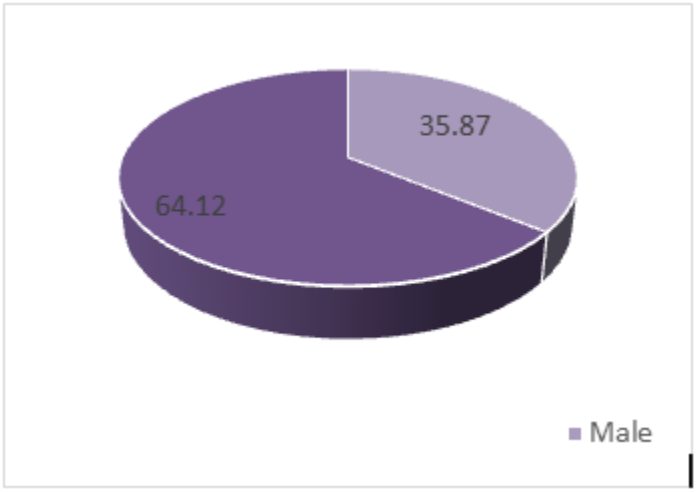

Table 1: Areas of learning with corresponding percentage of participants with correct responses to the respective questionnaire items-

S. No.	Areas of learning	Students with correct response(%)
1	a) Terminological framework in addiction medicine b) Regulation of substances with abuse potential under the Drugs & Cosmetics act, 1940	76.68 83.86
2	Identification of non-alcohol and non-opioid substances of abuse (nicotine, synthetic cannabinoids, volatile inhalants, ketamine, strychnine)	82.35
3	a) Identification of opioid toxicity and its management c) Long term management of opioid dependence	90.13 72.19
4	a) Management of alcohol withdrawal b) Treatment of alcohol dependence b) Management of toxic alcohol poisoning (methanol, ethylene glycol)	82.96 79.96 80.71
5	Smoking cessation	81.16

Figure 2: Distribution of participants based on the percentage of correct responses to the items of the questionnaire-

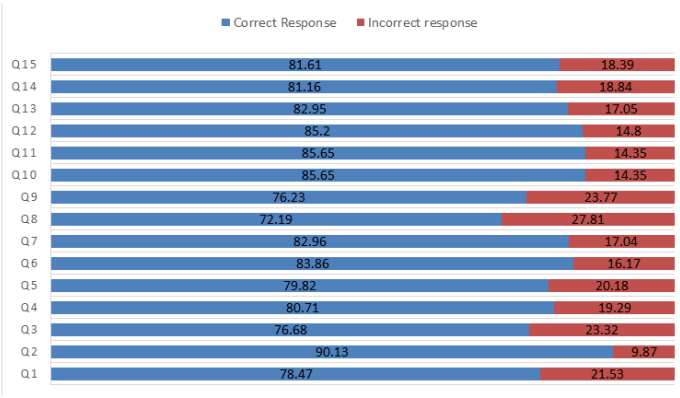

Table 2: Distribution of the study participants according to the knowledge gained after the training session-

Scoring	Categories	Number (%)
0-5	Poor Knowledge	23 (18.69)
6-10	Fair Knowledge	35 (28.45)
11-15	Good Knowledge	165 (73.99%)

DISCUSSION

The purpose of our study was to enhance awareness as well as assess the knowledge gained about substance abuse and de-addiction among the medical undergraduate students, following their learning session of one hour. The questionnaire, examining the students, was specially curated to test their understanding of the mechanisms of addiction and clinical strategies to treat the patient. It was

found that 73.99% of the total participants had good knowledge about drug abuse, detoxification and de-addiction strategies. We recognize that our findings do not exceed those reported by Akabuike et al., where 79.6% of the clinical students of Africa were reported to have good knowledge about drug abuse, majorly cocaine, followed by tramadol, cough syrup and amphetamine.[8] This highlights the requirement of continued improvement in both teaching strategies and clinical exposure of the medical students towards substance abuse.

Furthermore, the current study reported that 90.13% of the total participants could correctly identify the clinical cases of opioid overdose and toxicity, requiring naloxone rescue therapy. This finding is consistent with those reported by Moses et al. where significantly higher competency scores were obtained among the medical students who received Opioid Overdose Prevention and Response Training (OOPRT).[9]

Adding to the above data, approximately 85% of the total participants in our study, were able to recognize the mechanisms of abuse for substances like nicotine and alcohol, along with their first line detoxification regimens. Cape et al., in their study from New Zealand, reported 75% of the final year medical students to have good knowledge on topics such as safe levels of alcohol consumption and acute withdrawal effects from alcohol and benzodiazepines.[10] The more favorable outcome observed in this area of our study is encouraging, highlighting the constructive impact of such targeted educational interventions.

Our analysis also showed that not more than 76% of the total participants could correctly define and distinguish between relapse prevention and withdrawal management in patients of alcohol and opioid abuse. In contrast, Klimas et al. reported maximum improvement in knowledge among the Canadian participants, in relapse prevention, following their addiction medicine training session.[11] This underscores the need for increased emphasis on training the students about post- rehabilitation therapy.

Similar studies, as done by Landy et al. in UK, Ayu AP et al. in Indonesia, depicted enhanced competencies among medical students across the domains of knowledge, skills as well as attitude towards substance abuse and de-addiction.[12,13] The critical role of attitudinal competency in substance abuse training is duly acknowledged here, as it enables future physicians to treat their patients with enhanced empathy and reduced stigma. While the current study did not incorporate this critical dimension, we aim to address it in future surveys.

Our study population included undergraduate medical students only, however, there have been previous studies where such surveys were administered to pharmacy and nursing students. For instance, the results obtained by Jaber et al., Coleman et al. suggested relative lack of information with huge differences in the students' attitudes related to substance abuse, etiology of addiction and treatment issues.[14,15] For instance, approximately 44.8% of the pharmacy and 55.2% of nursing students had poor knowledge about addictive drugs, as reported by Qadhi OA et al. in Saudi Arabia.[16] When compared with our findings, where not more than 18.69% of the total participants had poor knowledge about substance abuse, these results underscore the importance of improving educational and skill development training among the allied health sciences students as well, along with their medical counterparts. Such an approach would ensure better integration of healthcare in our society.

Some studies, as reported by Nurmala et al., have documented negative attitudes among high school students, towards peer education on drug abuse, in HEY (Health Education for Youth) activities.[17] This encourages substance misuse education even at the school level, to deal with this societal challenge with greater efficiency.

In line with the studies conducted by Ram et al., a consensus had been reached that improving the pre-clinical curriculum is critical, whether through community based service learning electives, internet-based modules, and/or faculty development initiatives.[6] The National Medical Council (NMC) of India upgraded the medical undergraduate curriculum in 2018, to incorporate competency based training (PH1.21, PH1.22, PH1.23) on topics including substance abuse and de-addiction.[18] Such improved efforts towards training the future healthcare professionals promise a beneficial reduction in the morbidity and mortality related to substance use disorders.

We acknowledge some limitations to the current study. Firstly, a pre-test could not be administered due to the time constraint of one-hour for the learning session. Here, we recognize that a pre-test conduction could have aided in comparing students' knowledge before and after the learning session, thereby yielding better and more accurate results about the impact of such initiatives on medical education. Secondly, inclusion of skill and attitudinal competency assessment could have enhanced the authenticity of the results. Thirdly, as the data were obtained from a single tertiary-care teaching hospital, it could not be applied to the medical students globally. Additionally, due to a high male-female ratio among the students of this institute, the study might have under-reported the competency of budding female physicians. Overall, despite its shortcomings, this study emphasizes the importance of structured medical training about substance abuse in order to combat this societal challenge.

CONCLUSION

The findings of this study conclude that majority of the participating students had good knowledge about substance abuse and de-addiction. Substance abuse negatively impacts the biological, social as well as economic domains of human

life, causing serious health problems, family and societal disruption and heavy economic losses. It is well understood that if medical undergraduate students are better educated about the health repercussions, legal implications, and sociocultural setbacks due to substance abuse, future healthcare professionals will be better equipped to identify, reduce and treat substance abuse among their patients, thereby positively transforming the society as a whole.

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Availability of data and materials

Data, along with the questionnaire used during the study, will be available by emailing ishita18ag@gmail.com.

Authors' Contributions

- Ishita Agarwal*: corresponding author participated in the investigation, conceptualization, methodology, resources, supervision, validation, writing, reviewing, and editing.

- Kopal Sharma: participated in the investigation, conceptualization, methodology, writing, supervision, review, data collection and editing.

- Monica Jain: participated in the conceptualization, supervision, writing, reviewing and editing.

- Kavita Bhakar: participated in the data collection, writing and editing.

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

Ethics approval and consent to participate

The study protocol was reviewed and deemed exempt from formal approval by the Institutional Ethics Committee, as the research was conducted solely for educational purposes and did not involve any sensitive personal data.

Competing Interest

The authors declare that they have no competing interests.

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Review Article

Drug Update-Elinzanetant

Shubha Sharma*, Monica Jain, Muskan Jain*****

Abstract

Elinzanetant is a dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist currently in development for the treatment of vasomotor symptoms (VMS)—such as hot flashes and night sweats—in postmenopausal women. It exerts its therapeutic effect by blocking NK3 receptors, thereby inhibiting neurokinin B (NKB) activity on KNDy neurons in the hypothalamus, which are involved in thermoregulation.

Elinzanetant has shown consistent efficacy and safety across two Phase II and four Phase III clinical trials, demonstrating its potential in treating moderate to severe VMS associated with menopause as well as those induced by adjuvant endocrine therapy.

Keywords: Menopause; Vasomotor Symptoms; Hot Flashes, Neurokinin.

INTRODUCTION

Elinzanetant. also known as **NT-814**, is an investigational medication being developed to treat **vasomotor symptoms (VMS)** such as **hot flashes** and **night sweats** in postmenopausal women. In premenopausal women, it has been shown to suppress levels of **luteinizing hormone**, **estradiol**, and **progesterone** in a dose-dependent manner. Elinzanetant belongs to a novel class of drugs that act as **dual antagonists of neurokinin NK1 and NK3 receptors**. Its development is currently being led by **Bayer**, in collaboration with **GlaxoSmithKline** and **NeRRe Therapeutics[1].**

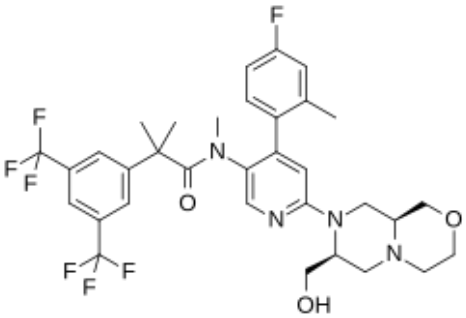
Elinzanetant is the first **dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist** in late-stage clinical development for the **non-hormonal, once-daily oral treatment** of **moderate-to-severe vasomotor symptoms (VMS)** associated with menopause. It targets the underlying pathophysiology of VMS by modulating **KNDy neurons**—a group of estrogen-sensitive neurons in the hypothalamus. With declining estrogen levels during menopause, these neurons become hypertrophic and trigger **hyperactivation of the thermoregulatory pathway**, leading to impaired body temperature control and the onset of VMS. In addition to reducing hot flashes and night sweats, elinzanetant may also help alleviate **menopause-related sleep disturbances**. Elinzanetant may also decrease sleep disturbances associated with menopause[1, 2].

About Vasomotor Symptoms

Vasomotor symptoms (VMS) commonly known as hot flashes are driven by the hyperactivation of the thermoregulatory pathway, a process mediated by the hypertrophy of KNDy neurons in the hypothalamus. This neuronal change is triggered by a decline in estrogen levels, which may occur naturally during menopause or as a result of medical interventions such as bilateral oophorectomy or endocrine therapy. In women undergoing endocrine therapy for the treatment or prevention of breast cancer, VMS are a common and distressing side effect, significantly affecting quality of life and treatment adherence. Currently, no approved therapies exist for managing VMS in this patient population.

Menopause is a natural transitional phase in a woman's life, marked by the **progressive decline of ovarian function**, typically occurring in the **late 40s to early 50s**. It can also result from **medical or surgical interventions**, such as treatments for **breast cancer**. The associated **hormonal decline** particularly in estrogen can trigger a range of symptoms that may significantly impact a woman's **health**, **quality of life**, **healthcare utilization**, and **work productivity**. Among the most commonly reported and disruptive symptoms during the menopausal transition are **vasomotor symptoms (VMS)**, **sleep disturbances** and **mood changes[1]**.

CHEMICAL STRUCTURE



Molecular formula: $C_{33}H_{35}F_7N_4O_3$

MW: 668.6 g/mol

IUPAC Name: *N*-[6-[(7*S*,9*aS*)-7-(hydroxymethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-pyrazino[2,1-c][1,4]oxazin-8-yl]-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-2-[3,5-bis(trifluoromethyl)phenyl]-*N*,2-dimethylpropanamide

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MECHANISM OF ACTION

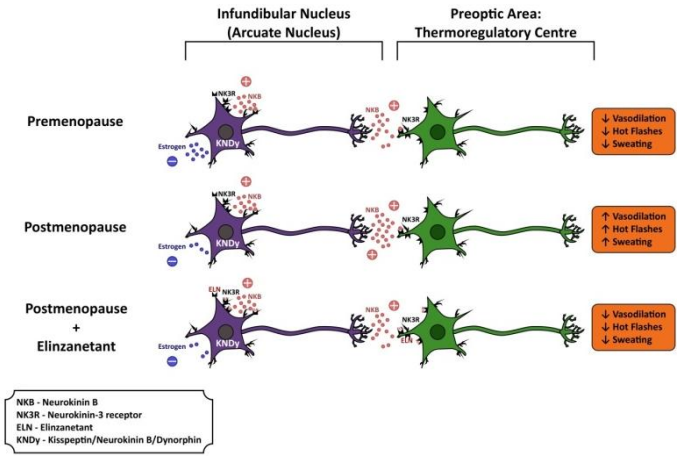

Figure 1: Mechanism of action of Elinzanetant

Elinzanetant is a non-hormonal therapy currently in development for the treatment of vasomotor symptoms (VMS) associated with menopause. It acts as a dual antagonist of neurokinin-1 (NK1) and neurokinin-3 (NK3) receptors, specifically targeting mechanisms involved in thermoregulation. Within the hypothalamus, KNDy neurons—which co-express kisspeptin, neurokinin B (NKB) and dynorphin—play a key role in regulating body temperature. During menopause, the decline in estrogen leads to hyperactivation of KNDy neurons, disrupting thermoregulatory control and resulting in symptoms such as hot flashes.

Elinzanetant works by blocking NK3 receptors, thereby inhibiting NKB activity on KNDy neurons and helping to restore thermoregulatory balance. The additional antagonism of NK1 receptors may enhance efficacy by further reducing vasodilation and heat-sensing neuronal activity, offering potential advantages over NK3 receptor antagonism alone[2].

DOSE

Therapeutic dose of elinzanetant is 120 mg once daily administration.

PHARMACOKINETICS

Elinzanetant is **rapidly absorbed** following oral administration, with an **elimination half-life (t½) of approximately 35 hours**. With **once-daily dosing**, **steady-state concentrations** are typically reached within **5 to 7 days** and drug accumulation remains **modest (<2-fold)**. Elinzanetant is primarily **metabolized by the cytochrome P450 enzyme CYP3A4**. Its **systemic clearance** is estimated at **7.26 L/h**, with a **central distribution volume** of **23.7 L** and a **peripheral distribution volume** of **168 L**. Co-administration with **high-fat meals** has been shown to **reduce the absorption rate** of elinzanetant[6].

ADVERSE EVENT AND TOLERABILITY

Elinzanetant was well tolerated in clinical trial phase-II and III with minimal side effects. The most common adverse drug reaction (ADR) in elinzanetant group was mild somnolence, Headache, fatigue and arthralgia. No severe adverse event was reported[4].

CLINICAL TRIALS

Two phase II clinical trials namely the RELENT-1 study (NCT02865538), (n=76) and the SWITCH-1 study (NCT03596762), (n=199) were performed on premenopausal women. The RELENT-1 study, received elinzanetant or placebo for 14 days in the doses of 50 mg/100 mg/150 mg/300 mG per day orally. Improvements in hot flash frequency, severity, and severity score were greatest in the 150 mg (84%) and 300 mg (66%) groups compared to placebo and 50 mg groups. The most common adverse events were mild somnolence and headaches, followed by diarrhea and pelvic pain. The rate of adverse events was highest in the 300 mg dose group. In the SWITCH-1 study, Elinzanetant/ placebo was given for 12 weeks in the doses of 120 mg/ 160 mg per day. The Insomnia Severity Index questionnaire (ISI), the Pittsburgh Sleep Quality Index (PSQI) total score, and the Menopause-specific Quality-of-Life questionnaire intervention (MenQol-I) were used for assessment of sleep and quality of life. Clinically meaningful improvements in ISI, PSQI and MenQol-I were observed in the 120 mg and 160 mg groups at weeks 4, 8, 12, and 16[2, 7].

The Phase III CT specifically OASIS program, currently comprises four Phase III studies: OASIS 1, 2, 3 and 4. OASIS 1 and 2 (NCT05042362 and NCT05099159), (n=396 and 400 respectively) investigated the efficacy and safety of elinzanetant for 26 weeks in the dose of 120 mg orally once daily or matching placebo for 12 weeks followed by elinzanetant, 120 mg, for 14 weeks. In both trials, reductions in VMS frequency and severity from baseline to weeks 4 and 12 were statistically significantly greater for elinzanetant vs placebo group[4]. The **OASIS 3 trial** (NCT05030584), which included **628 participants**, evaluated the **long-term safety and efficacy of elinzanetant over 52 weeks**. The results were **consistent with previous findings**, further supporting its **favorable safety profile**. Notably, there were **no reported cases of endometrial hyperplasia** or **endometrial malignant neoplasms**, and **no signals of hepatotoxicity** were observed during the study.[8]. The phase 3 OASIS 4 (NCT05030584) study for 52 weeks , demonstrated that elinzanetant, significantly reduced the frequency and severity of moderate to severe vasomotor symptoms (VMS) in women undergoing adjuvant endocrine therapy for hormone receptor–positive breast cancer. Improved sleep quality and menopause-related quality of life were reported by participants from baseline to weeks 4 and 12 compared with placebo. Elinzanetant's safety profile remained consistent, supporting its potential as a nonhormonal treatment option for managing VMS[9].

Abbreviations

ISI	:	Insomnia Severity Index questionnaire
MW	:	Molecular Weight
MenQol-I	:	Menopause-specific Quality-of-Life questionnaire intervention
NK	:	Neurokinin
PSQI	:	Pittsburgh Sleep Quality Index
VMS	:	Vasomotor symptoms

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Availability of data and materials

Data will be available by emailing shubhasharmajpr@gmail.com

Authors' Contributions

- Author1: Literature search, writing, and editing.

- Author2: Reviewing, and editing

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

Competing Interest

The authors declare that they have no competing interests.

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Review Article

Berdazimer Sodium

Jaya Sharma*, Monica Jain**

Abstract

Molluscum Contagiosum, caused by a pox virus is a contagious skin infection which can persist for months to years, resulting in individual's quality-of-life concerns as external lesions may be associated with discomfort, emotional distress, and social stigma, and they may also result in scarring after healing. It presents certain clinical challenges due to the limitations of existing treatment modalities. Berdazimer sodium 10.3% is an investigational medicine to be approved for this condition. This drug update explores its potential as a novel nitric oxide therapy; in revolutionising the management of Molluscum Contagiosum by describing all the clinical trial data. Possible applications of this novel and innovative therapeutic agent may significantly impact future research directions and the development of preventive strategies.

Keywords: Mollucum Contagiosum, Berdazimer gel 10.3%, Topical, Nitric Oxide

Introduction

Molluscum contagiosum (MC) is a common, mostly benign, and highly contagious viral skin infection caused by the double stranded DNA virus of the genus molluscipoxvirus (MCV) which belongs to the poxviridae family. MC is one of the top 50 most prevalent diseases occurring worldwide. MCV has been classified into four types as MCV1, MCV2, MCV3, and MCV4 of which MCV1 is more prevalent and affects more than 90% of children with MC whereas MCV4 has only been found in Asia and Australia. The clinically visible lesions called as mollusc, appear as small 2-5 mm diameter, skin-coloured to pink, elevated umbilicated papules which primarily affect young children, sexually active adults, and immunodeficient patients.[1-3]

The virus infects the epidermis either via skin-to-skin contact, autoinoculation (touching or scratching lesions), or contact with any contaminated items i.e., towels, toys, and other commonly used surfaces leading to the spread of lesions to other parts of the body as well. Once infected, the virus replicates specifically in the basal layer of epidermis, where infected cells rapidly proliferate leading to the development of aggregated molluscum bodies called as Henderson-Patterson bodies containing MCV virions as central core which manifests as umbilicated papules.[4] Appearance of MC lesions can be anywhere on the body but are typically found on the face, neck, limbs, abdomen and genital areas with the clinical presentation of 1 to 20 lesions in most people, yet in severe cases like in immunocompromised patients 100 lesions may be seen.[3]

Molluscum contagiosum infection can persist for months to years, resulting in quality-of-life concerns as external lesions may be associated with discomfort and psychosocial stigma, and scarring after resolution. Its highly contagious nature and concern for infecting others necessitates therapeutic intervention.[5,6]

Current Therapeutic Approaches

Current approaches involve various physical removal methods, like curettage, cryotherapy, and laser therapy but may post challenges such as pain and scarring, skin discolouration and also repeated doctor visits. Various oral medications like cimetidine and topical therapies such as Cantharidin, iodine, podophyllotoxin cream, salicylic acid, potassium hydroxide, tretinoin, and imiquimod. However, they can exhibit limitations because of reduced efficacy on facial Mollusca, also some topical agents are contraindicated for children due to potential toxicity or adverse events.[7]

FDA Approval of Berdazimer Sodium: A Milestone in Targeted Therapeutics

A recent advancement on January 5, 2024 came with the FDA approval of atopical, Nitric Oxide releasing prescription medication, Berdazimer gel (10.3%) (also known as SB206 12%, EPIH SPV, LLC,) for the treatment of adult and pediatric molluscum contagiosum, and it is the first at-home, under investigation medicine to be approved for this condition. This approval is based on the positive outcome & results demonstrated in two Phase 3 trials, B-SIMPLE 4 and B-SIMPLE 2, where it was observed that once-a-day use of topical berdazimer gel reduced the number of lesions, thereby confirming its safety and efficacy.[5,6]

Chemical Structure

Berdazimer sodium, the active ingredient, is a polymer made up of a polysiloxane backbone (Si-O-Si bonds) with

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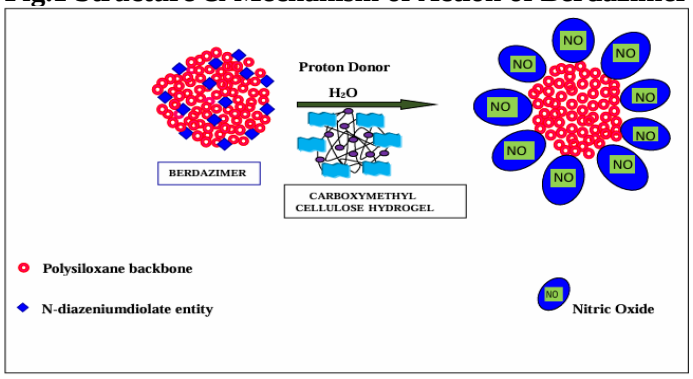
covalently attached N-diazeniumdiolate groups that serve as Nitric Oxide (NO) donors. Due to the insoluble nature of berdazimer sodium, the molecular formula, molecular mass, and average molecular weight range cannot be determined.[5] Fig.1

Empirical formula:
$[(C4H9N3NaO3.5Si)_3(C4H10NO1.5Si)1(SiO2)_6(HO0.5)_5]0.1$

Mechanism of Action

Berdazimer Sodium, a macromolecule, releases Nitric Oxide through exposure to proton donors like water, which will degrade the N-diazeniumdiolate entity. It is delivered in combination with a carboxymethyl cellulose hydrogel, which acts as a proton donor to facilitate site-specific drug delivery. Nitric oxide functions as both a short-lived immunomodulatory and as a direct broad-spectrum antimicrobial agent, which is released stably targeted to the skin lesions and thus provides localized immunity against foreign pathogens and simultaneously minimizing systemic exposure. Nitric oxide plays a regulatory functional role that affects NF-κB, immunomodulation, cytokine production, inflammation, and apoptosis mainly through S-nitrosylation of proteins resulting in viral DNA damage through nitrosative and oxidative stress. Nitric oxide also has cytotoxic functions and affects viral replication via reactive oxygen species and/or nitrogen molecules. Topical nitric oxide, therefore, serves as a novel therapeutic option, but it presents certain limitations in storage and safely delivering a stable form of nitric oxide to the target site of infection or inflammation.[8] Fig.1

Fig.1 Structure & Mechanism of Action of Berdazimer



Dosage and Administration

Berdazimer gel, 10.3% is supplied as two gel tubes namely Tube A Berdazimer gel (14gm) and Tube B Hydrogel (17gm) that are mixed on the basis of dosing guide; coadministration of the two components equally (0.5 ml) from both the tubes, the new chemical compound formed functions as a proton donor, causes the release of nitric oxide from the macromolecule berdazimer sodium. The gel is then applied by using a fingertip on the MC lesions superficially and is left to dry for 10 minutes after application. It can be self-applied by the patient or by caregiver once a day and does not require its removal post-application as compared to earlier treatments which were exclusively administered by the healthcare professionals.[9]

Efficacy and Safety (Table 1)

1. Molluscum Contagiosum

The FDA approval of Berdazimer gel 10.3% follows positive outcomes from various in vitro studies showing Berdazimer sodium (the active ingredient in berdazimer gel, 10.3%) having an antiviral and immunomodulatory activity against the molluscum contagiosum virus and simultaneously the results from various randomised clinical trials involving 1598 patients confirming its safety and efficacy.[10]

Phase II Trial

A Phase 2, dose-finding study involving both the pediatric and adult patients with molluscum contagiosum was done. It was found that once-daily application of berdazimer sodium 12% (equivalent to 10.3% berdazimer free base) is an appropriate candidate for advancement to Phase 3 clinical trials.[7,8,9]

Phase III Trial

Following this, a phase III multicentre, randomised, vehicle-controlled study evaluated the efficacy and safety of a treatment known as SB206 at a 10.3% concentration. B-SIMPLE 1, 2, and 4 were randomized, double-blind, vehicle-controlled, parallel-group, multicenter, Phase III studies of 10.3% berdazimer gel, conducted in the United States.[10]

B-SIMPLE 1 & 2

Integrated efficacy analysis of two phase III randomized (2:1) clinical trials (B-SIMPLE [Berdazimer Sodium In Molluscum Patients with Lesions] 1 and 2) concluded that with once-daily application of 10.3% berdazimer gel, there was greater MC complete clearance rates at week 12 vs vehicle (27.9% [132 of 473 patients] vs 20.9% [49 of 234 patients]; $P < .04$) supporting the potential efficacy of berdazimer gel as a treatment option for MC.[11]

B-SIMPLE 4

After discussions with the FDA a third phase III study was designed to confirm the efficacy and safety of topical 10.3% berdazimer gel, in comparison with the placebo gel, both applied once daily for up to 12 weeks in patients 6 months or older having 3 to 70 raised and palpable MC lesions. The B-SIMPLE 4 was a randomized (1:1), double-blind, vehicle controlled, parallel-group, multicentre, phase 3 clinical trial which enrolled 891 patients, conducted across 55 sites in the US to evaluate the efficacy and safety of 10.3% topical berdazimer gel.

Study medication was applied once daily as a thin layer to the top of all MC lesions by caregivers at clinic visits scheduled at baseline and at weeks 2, 4, 8, and 12, and rest of the days by the patients at home and were instructed to continue treating the lesion until the next scheduled visit, even if the lesion(s) get cleared.

At week 12, the Berdazimer group showed significantly higher complete lesion clearance (32.4%) as compared to the placebo group depicting more substantial reductions in lesion count than the placebo.The B-SIMPLE4 trial was instrumental in confirming Berdazimer's effectiveness and safety in the treatment of molluscum contagiosum. [12]

FDA Approval: Based on the results from three phase III clinical trials involving 1,598 patients, berdazimer gel received FDA approval in 2024 as a first-in-class, self- or caregiver-applied topical treatment for MC. [11]

2. External Genital and Perianal Warts

In a double-blind, randomized Phase 2 clinical trial involving 108 individuals with extragenital warts, SB206—berdazimer sodium combined with carboxymethyl cellulose hydrogel—was tested for its effectiveness. Participants were randomly divided in a 3:1 ratio to receive either SB206 at varying concentrations (4% once or twice daily, 8% once daily, or 12% once daily) or the vehicle alone. The results showed that a 12% concentration of SB206, applied once daily, was significantly more effective than the placebo, achieving a clearance rate of 33.3% compared to just 4.3%. A network meta-analysis found that SB206's effectiveness was on par with commonly used topical treatments such as imiquimod and podophyllotoxin. Despite these promising findings, larger and more rigorous studies are needed to fully evaluate SB206's potential in treating external genital warts.[13]

3. Acne Vulgaris

A Phase 2 randomized, double-blind controlled trial was conducted involving 150 participants to evaluate SB204 at 1% and 4% concentrations, compared to a vehicle, with participants evenly assigned in a 1:1:1 ratio. The findings showed a notable reduction in the number of non-inflammatory lesions from the beginning of the study to week 12 in the SB204 treatment groups as compared to the vehicle. Nonetheless, the investigator global assessment (IGA) scores did not reveal a statistically significant difference between the treatment groups. [14]

4. Atopic Dermatitis

SB414 at a 2% concentration has shown both antimicrobial and anti-inflammatory properties, exhibiting reduction in Th-2, Th-22, Th-1, and Th-17 related biomarker expression in mouse models with filaggrin deficiency suggesting that berdazimer sodium having immunomodulatory effects. [15]

5. Tinea Pedis

A Phase 2 randomized controlled trial was conducted enrolling 222 individuals diagnosed with interdigital tinea pedis. The study evaluated SB208 at 2%, 4%, and 16% concentrations in comparison to the vehicle control. The 4% and 16% formulations of SB208 showed significantly greater effectiveness than the vehicle. SB208 is being considered for future clinical trials for the treatment of Onychomycosis.[16] Various Randomized Control Trials of Berdazimer Sodium are tabulated in Table 1.

Table 1: Randomized Control Trials of Berdazimer Sodium for various conditions

Condition	Study (First Author, Year)	Trial Phase	Formulation / Dosing	Sample Size	Primary Endpoint	Efficacy Outcome	Safety
Molluscum Contagiosum	**Adelaide A. Hebert[11], 2020**	Phase 2	SB206 12% QD (once daily) (berdazimer sodium gel coadministered with hydrogel)	256 (aged 2–16)	Complete lesion clearance at 12 weeks	37.5% (18/48) vs. 18.2% (12/66) in vehicle group.	Mild to mode-rate application-site reactions; noticeable lesion changes as early as week 1.
	John Caleb B rowning[12], 2023	Phase 3 (B-SIMPLE 4)	Berdazimer gel 10.3% QD	891 (aged ≥6 months)	Complete lesion clearance at 12 weeks	32.4% (144/444) vs. 19.7% (88/447) in vehicle group.	Well-tolerated; mild transient application-site pain and erythema most common.
External Genital Warts	**Jung JM[13], 2020**	Phase 2	SB206 12% QD	108	Complete clearance of baseline lesions	33.3% vs. 4.3% in vehicle group.	Well-tolerated; comparable efficacy to traditional topical agents like imiquimod
Acne Vulgaris	**Baldwin H[14], 2016**	Phase 2	SB204 1% and 4% QD	150	Change in non-inflammatory lesion count	Significant reduction in lesion count; no significant difference in Investigator Global Assessment scores.	Safe and well-tolerated; no significant differences in IGA success rates between groups.

Atopic Dermatitis	**Guttman-Yassky E[15], 2020**	Phase 2	SB414 2%	48	**Antimicrobial activity** against *Staphylococcus aureus* and other skin flora	Rapid and broad-spectrum antimicrobial activity, Downregulation of inflammatory markers (e.g., IL-4, IL-13) in skin biopsies	Modest but statistically significant improvements in disease severity were observed in patients using SB206 compared to controls.
Tinea Pedis	**Elewski BE[16], 2018**	Phase 2	SB208 2%, 4%, and 16% QD	222	Negative fungal culture at end of treatment	4% and 16% concentrations showed statistically significant efficacy compared to vehicle.	Well-tolerated; supports further development for fungal infections.

Adverse Effects

The most common adverse reactions were localized skin reactions at the application site, such as pain, erythema, and pruritus. The reactions were predominantly mild to moderate in intensity, typically peaking during the second week of treatment and declining thereafter. [17,18] (Table 2.)

Table 2: Adverse effects reported with Berdazimer in various Randomized Control Trials

Type	Frequency	Adverse Effects
LOCALIZED	≥2% of Patients	**Application Site Reactions:** Pain (burning or prickling sensations) **(18.7%)** Erythema **(11.7%)** Pruritis **(5.7%)** Exfoliation **(5.0%)** Dermatitis **(4.9%)** Swelling **(3.5%)**
LOCALIZED	<2% of Patients	**Application Site Reactions:** Erosion **(1.6%)** Vesicles **(1.5%)** Discoloration **(1.5%)** Irritation **(1.2%)** Infection **(1.1%)**
SYSTEMIC		Pyrexia Vomiting Upper respiratory tract Infection Nasopharyngitis Headache Dysmenorrhea

Conclusion and Future Directions

Berdazimer's potential to revolutionise MC management is evident, providing a safe, effective, feasible and easy to use treatment option. Its superior efficacy, rapid clearance times, and patient's convenience in use marked a fundamental alteration in MC therapy, resulting in improved outcomes for both patients as well as healthcare systems.

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Case Report

Gastrointestinal Neuroectodermal Tumor (GNET)

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Abstract

Gastro neuroectodermal tumor (GNET), previously known as clear cell sarcoma-like tumor of the gastrointestinal tract, is a rare and aggressive malignant neoplasm arising from neural crest-derived cells. We present the case of a 64-year-old Female who presented with abdominal discomfort and intermittent episodes of nausea and vomiting since past 3 months. Imaging revealed thickened jejunal and ileal loops and histopathological examination confirmed GNET with characteristic features including S100 and SOX10 positivity. The patient underwent surgical resection. This case underscores the importance of considering GNET in the differential diagnosis of gastrointestinal tumors and highlights the role of immunohistochemistry in achieving an accurate diagnosis.

Keywords: Gastro neuroectodermal tumor, clear cell sarcoma

Introduction

Gastrointestinal Neuroectodermal tumors are an uncommon and poorly understood group of neoplasms. The term "gastroneuroectodermal" describes the histologic characteristics of these tumors, which exhibit a combination of epithelial, neural, and mesenchymal differentiation. They are rare in clinical practice, and their diagnosis often presents a challenge due to their unusual histopathologic features and nonspecific clinical symptoms. GNETs primarily affect adults, with a higher incidence observed in middle-aged individuals.

Case Report

A 64-Year-Old Female patient presented to the outpatient clinic with complaints of abdominal discomfort with significant weight loss over the past three months, and intermittent episodes of nausea and vomiting. Constipated since 3 days. There was no history of melena or hematochezia.

Physical examination revealed a moderately distended with diffusely painful abdomen. She had no significant past medical history.

Her vital signs were within normal limits, and laboratory investigations, including a complete blood count and liver function tests, were unremarkable. A contrast-enhanced abdominal CT scan revealed distended jejunal, ileal loop with wall thickening approximately 10 cms at transition zone in distal ileum.

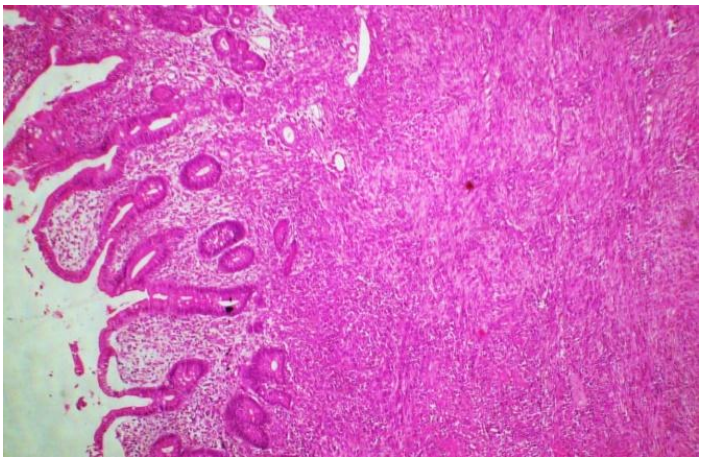
Diagnostic Workup

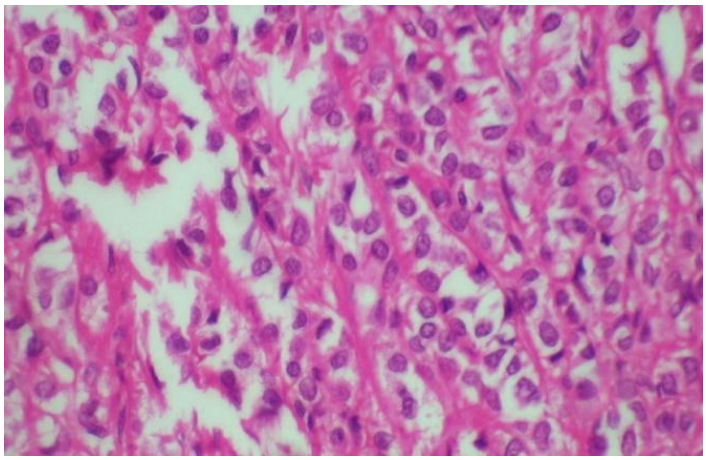
Complete resection of thickened jejunal and ileal loops was done, and histopathological examination showed infiltration of the stricture wall by the neoplastic cells arranged in cords and nests having vesicular chromatin and frequent mitosis.

No lymphovascular and perineural invasion seen.

Immunohistochemical staining was positive for vimentin, synaptophysin, S100 and SOX10 consistent with the diagnosis of gastrointestinal neuroectodermal tumor (GNET). Negative for LCA, CD117, DOG1, HMB45, Desmin, PanCK ruling out lymphoma, melanoma and GIST.

Molecular study (FISH) was advised for translocation t(12;22)(q13;q12).





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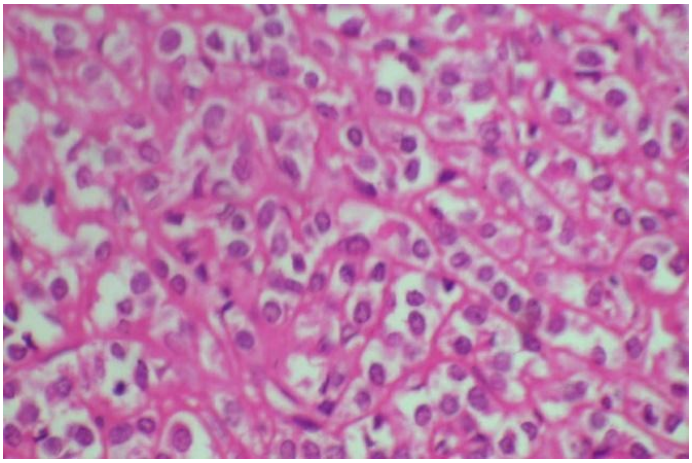

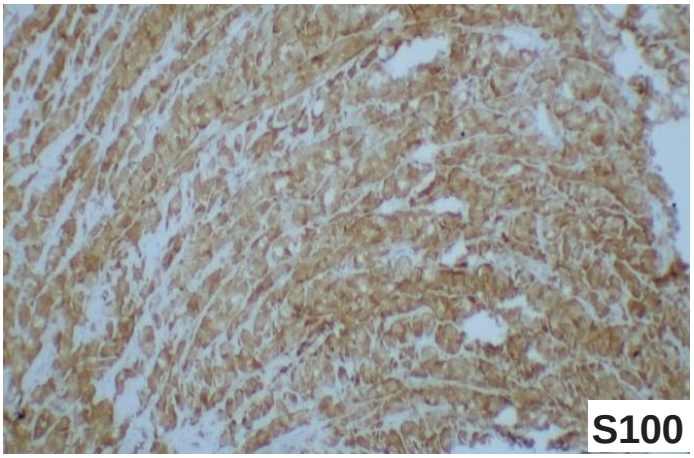

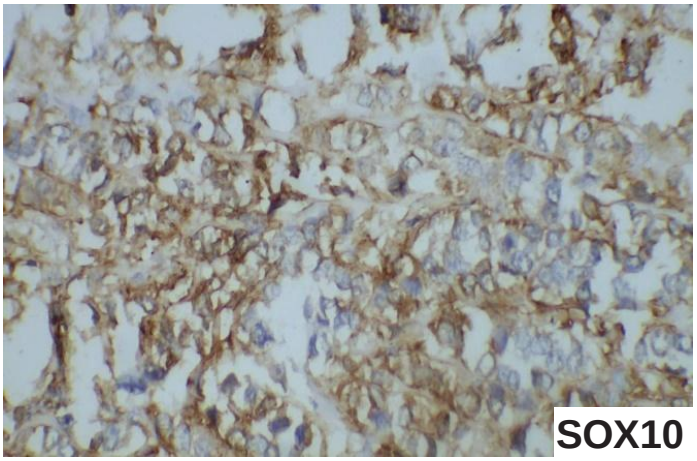

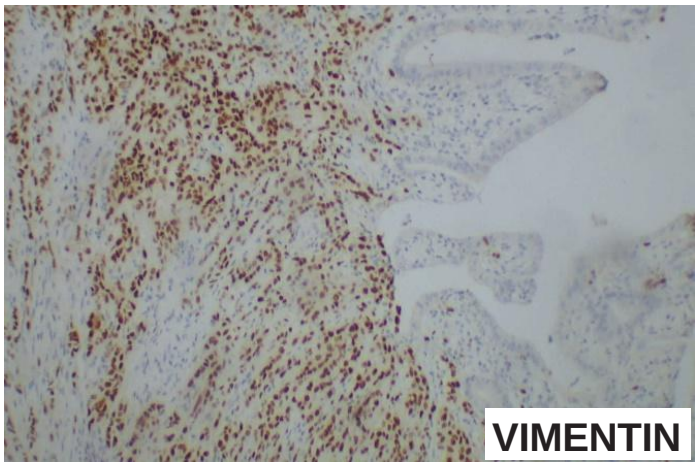

Discussion

GNET is the newly identified entity, which mimics GIST both clinically and histologically. However the treatment of both are discrete.

Therefore having the knowledge of this entity is essential to ensure institution of appropriate treatment to the patient.

The cell of origin of malignant gastroneuroectodermal tumors (GNETs) remains a topic of debate and investigation.

One plausible theory is that GNETs originate from a multipotent stem cell with the potential to differentiate into different cell types, including GI, neural, and ectodermal components.

In 2003 Zambrano et. al. described GNET as clear cell sarcoma (CCS).

Later on, by analyzing the CCS proportions for melanocytes markers,this tumor was first diagnosed as malignant GNET by Stockman et al.

GNET should be suspected in any tumor arising in the wall of the gastrointestinal tract (GIT) displaying an epithelioid or spindle cell population. Morphological differentials include CCS-GI, metastatic melanoma, gastrointestinal stromal tumor (GIST), synovial sarcoma and metastatic clear cell carcinoma.

It is important to differentiate GNET from GIST because effective target therapy for GIST is available,but not for the former.

Conclusion

Gastroneuroectodermal tumors are rare entities that can present a diagnostic challenge due to their nonspecific clinical presentation and complex histopathologic features. Early detection and complete surgical resection are key to improving outcomes.

While research into the molecular and genetic characteristics of GNETs is still evolving, the mixed nature of these tumors highlights the complexity of cancer stem cell biology and differentiation. Further investigation into the molecular mechanisms of these rare tumors could provide important insights into their origin and lead to more effective treatments.

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Availability of data and materials:

Data will be available by emailing dr.mansidixit@gmail.com

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-Author 1: participated in the investigation, conceptualization, methodology, diagnosis and editing

-Author 2*: participated in the investigation, resources, writing, reviewing, editing and is corresponding author

-Author 3: participated in the investigation, conceptualization, methodology and diagnosis

-Author 4: participated in the investigation, conceptualization, methodology and diagnosis

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